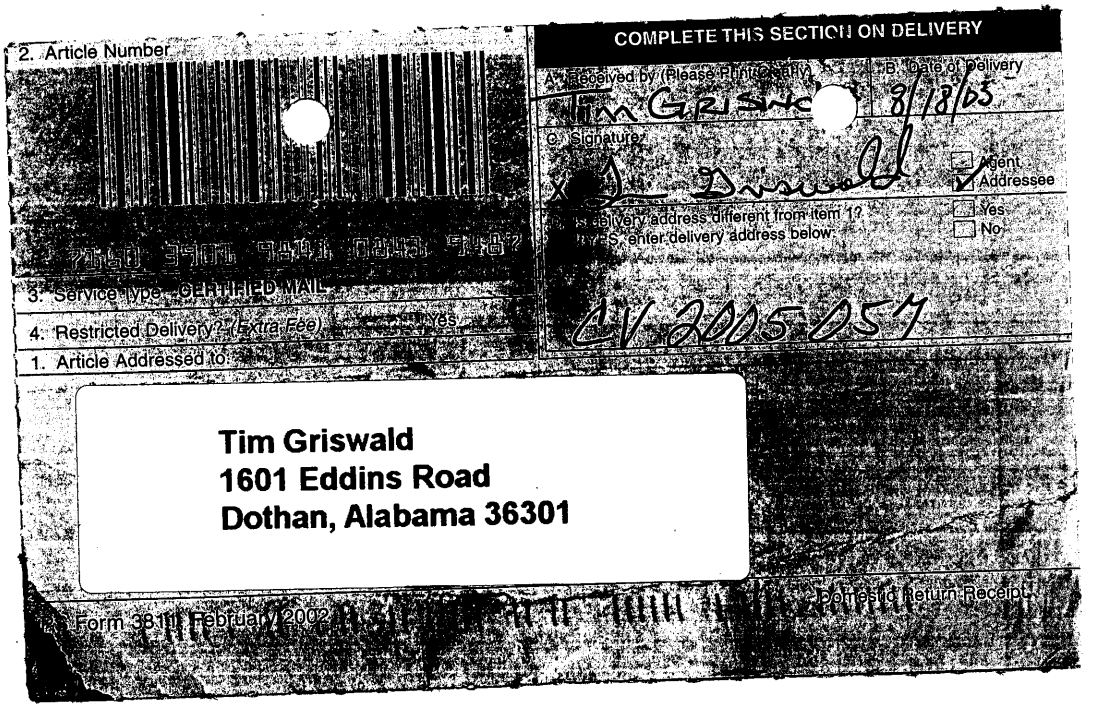
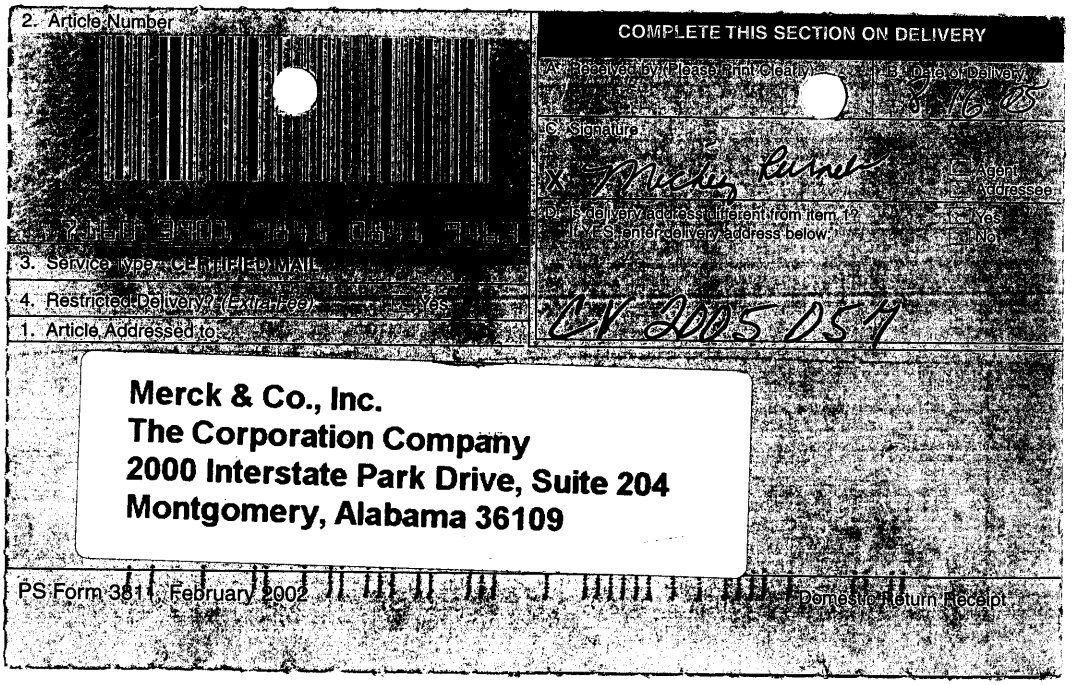




DEFENDANT'S EXHIBIT
A

State of Alabama
Unified Judicial System

Form ARCivP-93 Rev. 5/99

COVER SHEET
CIRCUIT COURT - CIVIL CASE
(Not For Domestic Relations Cases)

Case Number: CV 2005 00057
Date of Filing: Month Day Year
Judge Code:

GENERAL INFORMATION

IN THE CIRCUIT COURT OF Barbour County (Name of County), ALABAMA

T. Pawdon Beaty
Plaintiff

Merck & Co, Inc.
Defendant

FILED
AUG 12 2005
DAVID S. NIX, CLERK
BARBOUR COUNTY, ALABAMA

First Plaintiff: ☐ Business ☒ Individual ☐ Government ☐ Other

First Defendant: ☒ Business ☐ Individual ☐ Government ☐ Other

NATURE OF SUIT: Select primary cause of action, by checking box (check only one) that best characterizes your action:

TORTS: PERSONAL INJURY
- ☐ WDEA - Wrongful Death
- ☐ TONG - Negligence: General
- ☐ TOMV - Negligence: Motor Vehicle
- ☐ TOWA - Wantonness
- ☒ TOPL - Product Liability/AEMLD
- ☐ TOMM - Malpractice-Medical
- ☐ TOLM - Malpractice-Legal
- ☐ TOOM - Malpractice-Other
- ☐ TBFM - Fraud/Bad Faith/Misrepresentation
- ☐ TOXX - Other: _____

TORTS: PROPERTY INJURY
- ☐ TOPE - Personal Property
- ☐ TORE - Real Property

OTHER CIVIL FILINGS
- ☐ ABAN - Abandoned Automobile
- ☐ ACCT - Account & Nonmortgage
- ☐ APAA - Administrative Agency Appeal
- ☐ ADPA - Administrative Procedure Act
- ☐ ANPS - Adults in Need of Protective Services

OTHER CIVIL FILINGS (cont'd)
- ☐ MSXX - Birth/Death Certificate Modification/Bond Forfeiture Appeal/ Enforcement of Agency Subpoena/Petition to Preserve
- ☐ CVRT - Civil Rights
- ☐ COND - Condemnation/Eminent Domain/Right-of-Way
- ☐ CTMP - Contempt of Court
- ☐ CONT - Contract/Ejectment/Writ of Seizure
- ☐ TOCN - Conversion
- ☐ EQND - Equity Non-Damages Actions/Declaratory Judgment/Injunction Election Contest/Quiet Title/Sale For Division
- ☐ CVUD - Eviction Appeal/Unlawful Detainer
- ☐ FORJ - Foreign Judgment
- ☐ FORF - Fruits of Crime Forfeiture
- ☐ MSHC - Habeas Corpus/Extraordinary Writ/Mandamus/Prohibition
- ☐ PFAB - Protection From Abuse
- ☐ FELA - Railroad/Seaman (FELA)
- ☐ RPRO - Real Property
- ☐ WTEG - Will/Trust/Estate/Guardianship/Conservatorship
- ☐ COMP - Workers' Compensation
- ☐ CVXX - Miscellaneous Circuit Civil Case

ORIGIN (check one):
- F ☒ INITIAL FILING
- R ☐ REMANDED
- A ☐ APPEAL FROM DISTRICT COURT
- T ☐ TRANSFERRED FROM OTHER CIRCUIT COURT
- O ☐ OTHER: _____

HAS JURY TRIAL BEEN DEMANDED? ☒ YES ☐ NO

Note: Checking "Yes" does not constitute a demand for a jury trial. (See Rules 38 and 39, Ala.R.Civ.P, for procedure)

RELIEF REQUESTED: ☒ MONETARY AWARD REQUESTED ☐ NO MONETARY AWARD REQUESTED

ATTORNEY CODE: SIZ004

8/10/05
Date

Paul S.
Signature of Attorney/Party filing this form

MEDIATION REQUESTED: ☐ YES ☐ NO ☒ UNDECIDED

IN THE CIRCUIT COURT OF
BARBOUR COUNTY, ALABAMA
CLAYTON DIVISION

T. RAWDON BEATY, an Individual,	*	
	*	
Plaintiff.	*	
	*	
v.	*	**CASE NO.** CV 2005 057
	*	
MERCK & CO., INC., a foreign Corporation; TIM GRISWALD, an Individual; and fictitious Defendants A, B, C & D, being those persons, firms or Corporations whose fraud, scheme to defraud, and/or other wrongful conduct caused or contributed to the Plaintiff's injuries and damages, and whose true names and identities are presently unknown to Plaintiff, but will be substituted by amendment when ascertained,	*	**JURY TRIAL DEMANDED**
	*	
Defendants.	*	

SUMMONS

This service by certified mail of this summons is initiated upon the written request of Plaintiffs' attorney pursuant to the Alabama Rules of Civil Procedure.

NOTICE TO: **Merck & Co., Inc.**
The Corporation Company
2000 Interstate Park Drive, Ste 204
Montgomery, AL 36109

The Complaint which is attached to this summons is important and you must take immediate action to protect your rights. You are required to mail or hand deliver a copy of a written Answer, either admitting or denying each allegation in the Complaint to,

J. Paul Sizemore
BEASLEY, ALLEN, CROW, METHVIN, PORTIS & MILES, P.C.
Post Office Box 4160
Montgomery, Alabama 36103-4160

the attorney for the Plaintiffs. THIS ANSWER MUST BE MAILED OR DELIVERED WITHIN THIRTY (30) DAYS FROM THE DATE OF DELIVERY OF THIS SUMMONS AND COMPLAINT AS EVIDENCED BY THE RETURN RECEIPT, OR A JUDGMENT BY DEFAULT MAY BE ENTERED AGAINST YOU FOR THE MONEY OR OTHER THINGS DEMANDED IN THE COMPLAINT. You must also file the original of your Answer with the Clerk of this Court within a reasonable time afterward.

DATED: 08-12-05

David S. Nix
Circuit Clerk

IN THE CIRCUIT COURT OF
BARBOUR COUNTY, ALABAMA
CLAYTON DIVISION

T. RAWDON BEATY, an Individual,	*	
	*	
Plaintiff.	*	
	*	
v.	*	**CASE NO.** CV 2005 057
	*	
MERCK & CO., INC., a foreign Corporation; TIM GRISWALD, an Individual; and fictitious Defendants A, B, C & D, being those persons, firms or Corporations whose fraud, scheme to defraud, and/or other wrongful conduct caused or contributed to the Plaintiff's injuries and damages, and whose true names and identities are presently unknown to Plaintiff, but will be substituted by amendment when ascertained,	*	**JURY TRIAL DEMANDED**
	*	
Defendants.	*	

SUMMONS

This service by certified mail of this summons is initiated upon the written request of Plaintiffs' attorney pursuant to the Alabama Rules of Civil Procedure.

NOTICE TO: **Tim Griswald**
1601 Eddins Road
Dothan, AL 36301

The Complaint which is attached to this summons is important and you must take immediate action to protect your rights. You are required to mail or hand deliver a copy of a written Answer, either admitting or denying each allegation in the Complaint to,

J. Paul Sizemore
BEASLEY, ALLEN, CROW, METHVIN, PORTIS & MILES, P.C.
Post Office Box 4160
Montgomery, Alabama 36103-4160

the attorney for the Plaintiffs. THIS ANSWER MUST BE MAILED OR DELIVERED WITHIN THIRTY (30) DAYS FROM THE DATE OF DELIVERY OF THIS SUMMONS AND COMPLAINT AS EVIDENCED BY THE RETURN RECEIPT, OR A JUDGMENT BY DEFAULT MAY BE ENTERED AGAINST YOU FOR THE MONEY OR OTHER THINGS DEMANDED IN THE COMPLAINT. You must also file the original of your Answer with the Clerk of this Court within a reasonable time afterward.

DATED: 08-12-05

David S. Nix
Circuit Clerk

IN THE CIRCUIT COURT OF
BARBOUR COUNTY, ALABAMA
CLAYTON DIVISION

T. RAWDON BEATY, an Individual, *

Plaintiff. *

v. * **CASE NO.** CV 2005057

MERCK & CO., INC., a foreign Corporation; TIM GRISWALD, an Individual; and fictitious Defendants A, B, C & D, being those persons, firms or Corporations whose fraud, scheme to defraud, and/or other wrongful conduct caused or contributed to the Plaintiff's injuries and damages, and whose true names and identities are presently unknown to Plaintiff, but will be substituted by amendment when ascertained, * **JURY TRIAL DEMANDED**

Defendants. *

COMPLAINT

COMES NOW, Theatus Rawdon Beaty, ("Plaintiff"), complaining of Merck & Co., Inc., individual sales representative Tim Griswald, and fictitious Defendants A, B, C & D, ("Defendants"), and for Plaintiff's cause of action against the Defendants states as follows:

Statement Of The Parties

1. Plaintiff Rawdon Beaty is over the age of 19 years and is a resident of Barbour County, Alabama.

2. Plaintiff was prescribed and used the prescription medication VIOXX (Rofecoxib). This a civil action seeks monetary damages for personal injuries caused by the prescription medication VIOXX (Rofecoxib) ingested by Plaintiff.

3. Defendant Merck & Co., Inc. (hereinafter referred to as "Merck"), is incorporated in the State of New Jersey and has its principal place of business in White House Station, New Jersey. At all times relevant herein, Merck was in the business of designing, testing, manufacturing, labeling, advertising, marketing, promoting, selling and distributing pharmaceuticals and other products, including VIOXX. Merck does business by agent in Alabama and, on information and belief, at all times relevant, advertised, marketed, promoted, sold and/or distributed VIOXX in Barbour County, Alabama. Defendant Merck can be served through its registered agent: Corporation Process Company, 2000 Interstate Park Drive, Suite 204, Montgomery, AL 36109.

4. Based upon information and belief, Defendant Tim Griswald is a sales representative for Defendant Merck, and is a resident of Houston County, Alabama. Defendant Tim Griswald can be served at his home address: 1601 Eddins Road, Dothan, AL 36301.

5. Fictitious Defendants A, B, C & D, are other legal persons (including retailers, pharmacies, sales representatives and manufacturers) who manufactured, labeled, advertised, marketed, promoted, sold and/or distributed VIOXX in Alabama.

6. When the word "Defendants" is used herein, it is meant to refer to all real and fictitious Defendants mentioned in the style of this Complaint, all of whom are jointly and severally liable to Plaintiff for Plaintiff's injuries.

7. At all times material to this complaint, each Defendant acted as an agent for each of the other Defendants, within the course and scope of the agency, regarding the acts and omissions alleged herein, and are therefore jointly and severally liable to Plaintiff for Plaintiff's injuries.

Statement Of The Facts

8. This is a civil action brought by the Plaintiff, Rawdon Beaty, who was prescribed and used the prescription medication VIOXX (Rofecoxib) and as a result suffered from deep venous thrombosis (DVT) of his right lower leg.

9. Personal jurisdiction and subject matter jurisdiction are appropriate in this court to all Defendants, as all Defendants have sold VIOXX in Alabama, in or near Barbour County, either directly or by agent, with the actual or constructive knowledge that the VIOXX they sold would ultimately be ingested by the Plaintiff, Rawdon Beaty, in Barbour County, the Plaintiff's county of residence, and therefore all Defendants have thus availed themselves of this jurisdiction.

10. The Defendants have sold VIOXX in Alabama, in or near Barbour County, either directly or by agent, with knowledge, actual or constructive, that the VIOXX they sold would ultimately be ingested by the Plaintiff, Rawdon Beaty, in Barbour County, the Plaintiff's county of residence, and that any damage or injury to Rawdon Beaty that may result from his use of VIOXX, including deep vein thrombosis, would result from his ingestion of VIOXX in Barbour County. Thus venue is therefore proper in Barbour County as to all Defendants pursuant to Ala. Code Ann. § 6-3-2. The claims of the Plaintiff herein satisfy the jurisdictional amount of this Court.

11. VIOXX (Rofecoxib) is a prescription drug designed to treat pain through reduced inflammation; VIOXX (Rofecoxib) is a cox-2 selective non-steroidal anti-inflammatory agent (NSAID). Defendants did manufacture, design, package, market, sell and distribute this drug. The Defendants encouraged the use of this drug through an aggressive marketing campaign, including through its detail sales representatives and direct-to-consumers. Defendants

misrepresented the safety and effectiveness of this drug and concealed or understated its dangerous side effects. Defendants' actions combined and contributed to cause Plaintiff's injuries, and thus are jointly and severally liable.

12. At all times relevant hereto, Defendants actually knew of the defective nature of their product as herein set forth, yet continued to design, manufacture, market, distribute and sell their product so as to maximize sales and profits at the expense of the general public's health and safety in conscious disregard of the foreseeable harm caused by these products. Defendants' conduct exhibits such an entire want of care as to establish that their actions were a result of fraud, ill will, recklessness, gross negligence or willful and intentional disregard to the Plaintiff's individual rights, and hence punitive damages are appropriate.

13. Rawdon Beaty was prescribed and used the prescription medication VIOXX (Rofecoxib) and as a result suffered deep venous thrombosis (DVT) in the popliteal vein of his right leg on October 11, 2004. Rawdon Beaty ingested the prescription medication VIOXX (Rofecoxib) in Barbour County, Alabama and the damage and injuries resulting from Rawdon Beaty's use of the prescription medication VIOXX (Rofecoxib) occurred in Barbour County, Alabama.

COUNT I – AEMLD (ALABAMA EXTENDED MANUFACTURER'S LIABILITY DOCTRINE)

14. Plaintiff alleges all prior paragraphs of this complaint as if fully set out herein.

15. Plaintiff's claims are brought pursuant to the Alabama Extended Manufacturer's Liability Doctrine. The pharmaceutical drug VIOXX (Rofecoxib), designed, manufactured, sold and/or supplied by Defendants, was placed into the stream of commerce in a defective and unreasonably dangerous condition, as designed, taking into account the utility of the product and

the risk involved in its use, and Defendants' product did reach Plaintiff without substantial change in the condition in which it was sold.

16. The pharmaceutical drug VIOXX (Rofecoxib), designed, manufactured, distributed, sold and/or supplied by Defendants, was defective due to inadequate testing.

17. Further, the pharmaceutical drug VIOXX (Rofecoxib), designed, manufactured, distributed, sold and/or supplied by Defendants, was defective in its marketing due to inadequate warnings or instructions, independently and when coupled with its aggressive marketing campaign.

18. Additionally, Defendants failed to provide timely and adequate warnings or instructions after the manufacturer knew of the risk of injury from VIOXX (Rofecoxib). Plaintiff's injuries, as hereinbefore described, were the proximate result of the defective condition of VIOXX (Rofecoxib) which was unreasonably dangerous to Plaintiff as the ultimate consumer when put to its intended use.

WHEREFORE, the Plaintiff demands judgment against Defendants in such an amount of compensatory and punitive damages as a jury deems reasonable, plus cost.

COUNT II – NEGLIGENCE

19. Plaintiff realleges all prior paragraphs of this complaint as if fully set out herein.

20. Defendants had a duty to exercise reasonable care in the design, manufacture, marketing, sale, testing and/or distribution of VIOXX (Rofecoxib) into the stream of commerce. Defendants failed to exercise ordinary care in the design, manufacture, marketing, sale, testing and/or distribution of VIOXX (Rofecoxib) into the stream of commerce. Defendants knew or

should have known that VIOXX (Rofecoxib) created an unreasonable risk of bodily harm or injury.

21. Despite the fact that the Defendants knew or should have known that VIOXX (Rofecoxib) caused unreasonably, dangerous side effects which many users would be unable to remedy by any means, the Defendants continued to market VIOXX (Rofecoxib) to the consuming public when there were adequate and safer alternative methods of treatment or opportunities for more meaningful warnings.

22. Defendants knew or should have known that consumers such as the Plaintiff would foreseeably suffer injury as a result of the Defendants' failure to exercise ordinary care as described herein. Defendants' negligence was a contributing cause of Plaintiff's injuries and Plaintiff's economic and non-economic loss.

WHEREFORE, Plaintiff demands judgment against Defendants in such an amount of compensatory and punitive damages as a jury deems reasonable, plus cost.

COUNT III – BREACH OF EXPRESS WARRANTY

23. Plaintiff realleges all prior paragraphs of this complaint as if fully set out hereto.

24. Defendants made express representations to Plaintiff relative to its product, VIOXX (Rofecoxib).

25. Defendant Merck, by and through their detail sales representatives and managers, made representations regarding the safety and efficacy of its product, VIOXX (Rofecoxib).

26. VIOXX (Rofecoxib) does not conform to the express representations made to the Plaintiff.

27. VIOXX (Rofecoxib) does not conform to the express representations made by Defendant Merck's agents/sales representatives.

28. Defendants' conduct in this matter was a contributing cause of injuries and damages suffered by Plaintiff.

WHEREFORE, Plaintiff demands judgment against the Defendants in such an amount of compensatory and punitive damages as a jury deems reasonable, plus cost.

COUNT IV – BREACH OF IMPLIED WARRANTY

29. Plaintiff realleges all prior paragraphs of the Complaint as if fully set out herein.

30. At the time Defendants marketed, sold and distributed VIOXX (Rofecoxib) for use by the general consuming public, including Plaintiff, Defendants knew of the use for which VIOXX (Rofecoxib) was intended and impliedly warranted the product to be of merchantable quality, and safe and fit for such use.

31. Plaintiff reasonably relied upon the skill and judgment of the Defendants as to whether VIOXX (Rofecoxib) was of merchantable quality, and safe and fit for its intended use.

32. Contrary to such implied warranty, VIOXX (Rofecoxib) was not of merchantable quality, or safe or fit for its intended use, because the product was and is unreasonably dangerous and unfit for the ordinary purposes for which they were intended and used as described above.

33. Defendants' conduct in this regard was a contributing cause of the Plaintiff's injuries and damages.

WHEREFORE, the Plaintiff demands judgment against Defendants in such an amount of compensatory and punitive damages as a jury deems reasonable, plus cost.

COUNT V – FRAUD

34. Plaintiff realleges all prior paragraphs of the Complaint as if fully set out herein.

35. Defendants negligently, recklessly, intentionally and fraudulently made material misrepresentations that VIOXX (Rofecoxib) was safe and effective. Defendants represented VIOXX (Rofecoxib) as safe so that the general consuming public, including Plaintiff, would rely upon said representations when purchasing said product.

36. Prior to and following the introduction of VIOXX (Rofecoxib) into the market as a prescribable pharmaceutical medication, Defendants set in motion a campaign to market its product. Defendants' representations made concerning VIOXX (Rofecoxib) as a safe and effective drug were made so that Plaintiff and the general consuming public would rely on said representations and take this drug. In fact, Plaintiff did rely on Defendants' representations in this regard.

37. At the time Defendants made these representations, it was aware that these representations were false and/or made these representations with reckless disregard to their truth. As a result of Defendants' fraud and misrepresentation, Plaintiff suffered injuries and damages.

WHEREFORE, the Plaintiff demands judgment against Defendants in such an amount of compensatory and punitive damages as a jury deems reasonable, plus cost.

COUNT VI – FRAUDULENT MISREPRESENTATION

38. Plaintiff re-alleges and incorporates the original complaint and all prior paragraphs of this amended complaint as if fully set out herein.

39. Merck trained its sales representatives, through programs such as the "VIOXX Obstacle Dodge Ball Program," the "Obstacle Response Guide for VIOXX" and "Top Ten Obstacle Handlers" to misstate and misrepresent the truly dangerous nature of VIOXX to prescribing physicians.

40. These programs were specifically designed and promulgated by Defendant Merck to train Merck sales representatives such as the individual Defendant Tim Griswald to mislead prescribing physicians about the safety of VIOXX.

41. These programs were specifically designed and promulgated by Merck to mislead prescribing physicians about the life threatening side effects, including myocardial infarction, of VIOXX.

42. Merck trained its sales representative force, including Tim Griswald, to utilize its "Dodge Ball" and "Obstacle Avoidance" programs during the sales representatives' interactions with or "calls" upon prescribing physicians.

43. These programs were utilized by sales representatives Tim Griswald to "dodge" relevant safety questions by physicians to whom they sold VIOXX. Indeed, these programs provide specific responses and representations that are to be made by Merck sales representatives to physicians during sales calls or in response to physician questions. These Merck mandated responses misrepresented the safety of VIOXX.

44. The VIOXX Obstacle Dodge Ball Program identifies and categorizes physician safety questions as "obstacles" to Merck's sales force. (Exhibit A). The "Dodge Ball" program specifically instructs sales representatives, including Tim Griswald, to "dodge" these physician safety related questions/obstacles. Indeed, the last few pages of the "Dodge Ball" instruction manual simply state "DODGE," "DODGE," and "DODGE." *Id.* The safety questions to be

"dodged" by sales representatives, including Tim Griswald, include, inter alia, questions such as, "I am concerned about the cardiovascular effects of VIOXX;" and "The competition has been in my office telling me that the incidence of heart attacks is greater with Vioxx than Celebrex." *Id.*

45. Additional sales representative guidelines provide specific answers to physician questions/obstacles (such as those noted above) that were to be recited by sales representatives, including Tim Griswald. (Exhibits B and C). Exhibit C outlines the "Top Ten Obstacle Handlers" for sales representatives (Exhibit C). The top three "obstacles" listed on the sales guidelines are physician safety questions involving VIOXX related "Cardiovascular Events." (Exhibit C). Sales representatives, including Tim Griswald, are thereafter provided with specific misrepresentations to make to the concerned physicians about the safety of VIOXX. For example, bulletins from Merck to its sales representatives state, "in response to recent published reports about VIOXX on May 1, 2000, we provided you with an approved verbal response to use to address customers questions around the incidence rate of MI's [myocardial infarctions] on patients taking VIOXX…" (Exhibit D: Bulletin for Vioxx: New PIRs Relative to Vioxx GI Outcomes Research Study.) Sales representatives, such as Tim Griswald, were therefore required to misrepresent that VIOXX does not increase the rate of myocardial infarctions' when compared with NSAID's. This misrepresentation is false and inaccurate, yet was intentionally, knowingly, recklessly, wantonly and/or negligently made to treating physicians, including the Plaintiff's prescribing physician, by the individually named sales representative, Tim Griswald. (Exhibit C, Obstacle Response 38; and Exhibit E, page 7; "Bulletin for VIOXX")

46. Merck's sales representatives, specifically Tim Griswald, utilized the misrepresentations contained in the obstacle avoidance programs to mislead Plaintiff's treating

physician concerning the safety of VIOXX and the occurrence of life threatening side effects, such as myocardial infarctions, from the usage of VIOXX.

47. Merck and the individually named sales representatives further misrepresented the safety of VIOXX to prescribing physicians by providing written literature to the doctors that contained false statements about the safety of VIOXX. Such literature would be forwarded to the physician who posed questions/obstacles to the sales representatives after the sales representatives had concluded their meeting with the physicians. Exhibit G is the specific "In Response To Your Questions" follow-up literature that misrepresents the cardiovascular safety of VIOXX. (Exhibit G; " In Response To Your Questions: Cardiovascular System.")

48. Sales representatives, including Tim Griswald, were also ordered to send follow-up letters to physicians with whom they met who had posed questions/obstacles. Exhibit H is an example of a form sales representative letter to a questioning physician that misrepresents that VIOXX does not increase the risk of adverse cardiovascular events in users. (Exhibit H.)

49. The culture of misrepresenting the safety of VIOXX by Merck and its sales representatives, including Tim Griswald, was so prevalent that the false and misleading "Obstacle Responses" used by the sales force were manipulated and altered in response to media scrutiny concerning the cardiovascular safety of VIOXX. (Exhibit I: "Action Required: Response to New York Times Article" and Exhibit J: "Action Required" REVISED Response to New York Times Article") Merck sales representatives utilized such Obstacle Response Revisions to continually mislead prescribing physicians, including the Plaintiff's prescribing physician, about the safety hazards of VIOXX.

50. The underlying inducement for both Merck and its sales representatives, including Tim Griswald, to make repeated misrepresentations to physicians about the safety of VIOXX

was, and still is, money. The more doctors prescribing VIOXX, the more money Merck made. The more doctors the sales representatives, such as Tim Griswald, cajoled into prescribing VIOXX, the more money and non-monetary bonuses the sales representatives received. (Exhibits K: "Field Incentive Plan for VIOXX"; and L: "Field Incentive Plan for VIOXX.") Thus, sales representatives, such as Tim Griswald, had a financial interest in propagating and promulgating the false and misleading information (i.e., obstacle responses) outlined above to as many prescribing physicians as possible, including the Plaintiff's prescribing physician.

51. Both the Plaintiff and his prescribing physician reasonably relied, to their detriment, upon the false oral and written misrepresentations of Defendant Merck and its sales representatives, including Tim Griswald, concerning the safety of VIOXX and the absence of adverse cardiovascular events in users. Such reasonable reliance induced Plaintiff's treating physician to prescribe him VIOXX and further induced the Plaintiff to utilize the dangerous drug VIOXX. As a direct and proximate result of the Plaintiff's usage of VIOXX he suffered a stroke. Such event has caused the Plaintiff great pain and suffering, mental anguish, expense and will shorten his life expectancy.

DAMAGES

52. Upon the trial of this case, it will be shown that Plaintiff was caused to sustain injuries and damages as a direct and proximate result of Defendants' conduct individually, separately, and in concert; and Plaintiff will respectfully request the Court and jury to determine the amount of loss Plaintiff has suffered and incurred, in the past and in the future, not only from a financial standpoint, but also in terms of anxiety, distress, fear, pain, suffering and distress secondary to any physical injury and damages.

53. At all times relevant hereto, Defendants actually knew of the defective nature of their product as herein set forth and continued to design, manufacture, market, distribute and sell their product so as to maximize sales and profits at the expense of the public health and safety in conscious disregard of the foreseeable harm caused by this product. Defendants' conduct exhibits such an entire want of care as to establish that their actions were a result of fraud, ill-will, recklessness, gross negligence, or willful or intentional disregard of the Plaintiff's individual rights. The Plaintiff, therefore, is entitled to punitive damages from the corporate Defendant.

54. Plaintiff hereby requests a trial by jury on all issues in this case and hereby tenders the requisite jury fee simultaneously with this Complaint.

WHEREFORE, PREMISES CONSIDERED, Plaintiff prays that the Defendants be cited to appear and answer herein; that upon final trial herein, Plaintiff recovers damages as set forth above from Defendants, including cost of Court, pre-judgment and post-judgment interest at the legal rates, and punitive damages, and that Plaintiff has such other and further relief, both general and special, at law and in equity, to which Plaintiff may be justly entitled under the facts and attending circumstances.

DEMAND FOR JURY TRIAL

COME NOW Plaintiff and demands a trial by jury on all issues presented herein.

Signed this 10 day of August, 2005.

ANDY D. BIRCHFIELD, JR. (BIR006)
J. PAUL SIZEMORE (SIZ004)
Attorneys for Plaintiff

OF COUNSEL:

BEASLEY, ALLEN, CROW, METHVIN,
PORTIS & MILES, P.C.
Post Office Box 4160
Montgomery, Alabama 36103-4160
Phone (334) 269-2343
Fax (334) 223-1236

CERTIFICATE OF SERVICE

I hereby certify that I have filed a copy of the foregoing document with the Circuit Clerk along with the Summons and Complaint on this the 10 day of August, 2005.

EXHIBITS ATTACHED

IN THE CIRCUIT COURT OF
BARBOUR COUNTY, ALABAMA
CLAYTON DIVISION

T. RAWDON BEATY, an Individual,

Plaintiff.

v.

MERCK & CO., INC., a foreign Corporation; TIM GRISWALD, an Individual; and fictitious Defendants A, B, C & D, being those persons, firms or Corporations whose fraud, scheme to defraud, and/or other wrongful conduct caused or contributed to the Plaintiff's injuries and damages, and whose true names and identities are presently unknown to Plaintiff, but will be substituted by amendment when ascertained,

Defendants.

CASE NO. CV 2005 057

JURY TRIAL DEMANDED

PLAINTIFF'S FIRST SET OF INTERROGATORIES AND REQUESTS FOR PRODUCTION OF DOCUMENTS TO DEFENDANT MERCK & COMPANY, INC.

Pursuant to Rule 33 and 34 of the *Alabama Rules of Civil Procedure*, the Plaintiff propounds the following interrogatories and requests for production of documents to be answered by Defendant Merck & Company, Inc, a Party Defendant, in the manner and form prescribed by law:

Definitions

1. "Documents" shall mean writing of every kind, source and authorship, both originals and all non-identical copies thereof, in your possession, custody or control, or known by you to exist, irrespective of whether the writing is one intended for or transmitted internally

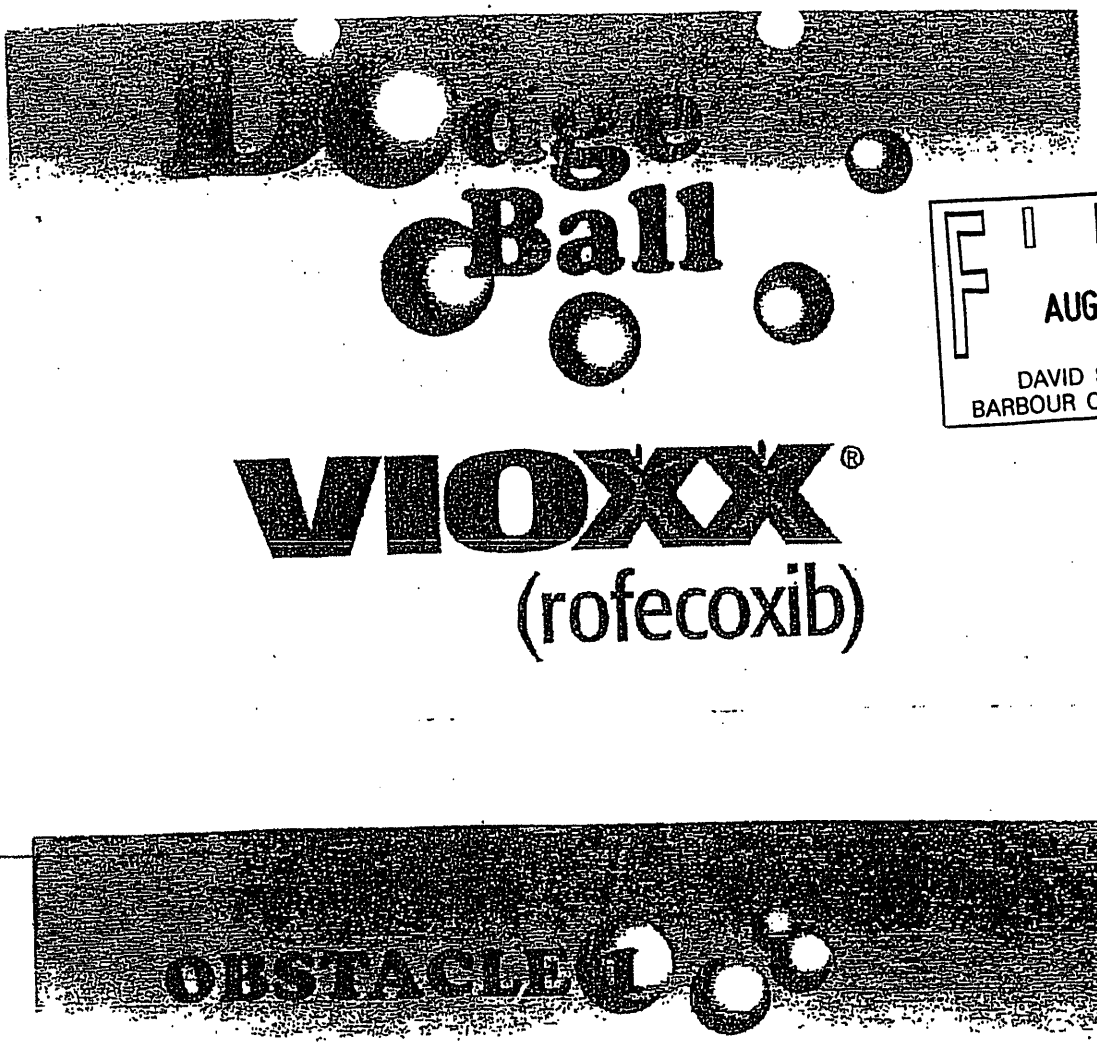
other financial institution or institutional investment corporation, whether for purposes of stock/bond underwriting, pursuant to financing conditions of underwriting or not, or for general dissemination of product news.

ANDY D. BIRCHFIELD, JR. (BIR006)
J. PAUL SIZEMORE (SIZ004)
Attorneys for Plaintiff

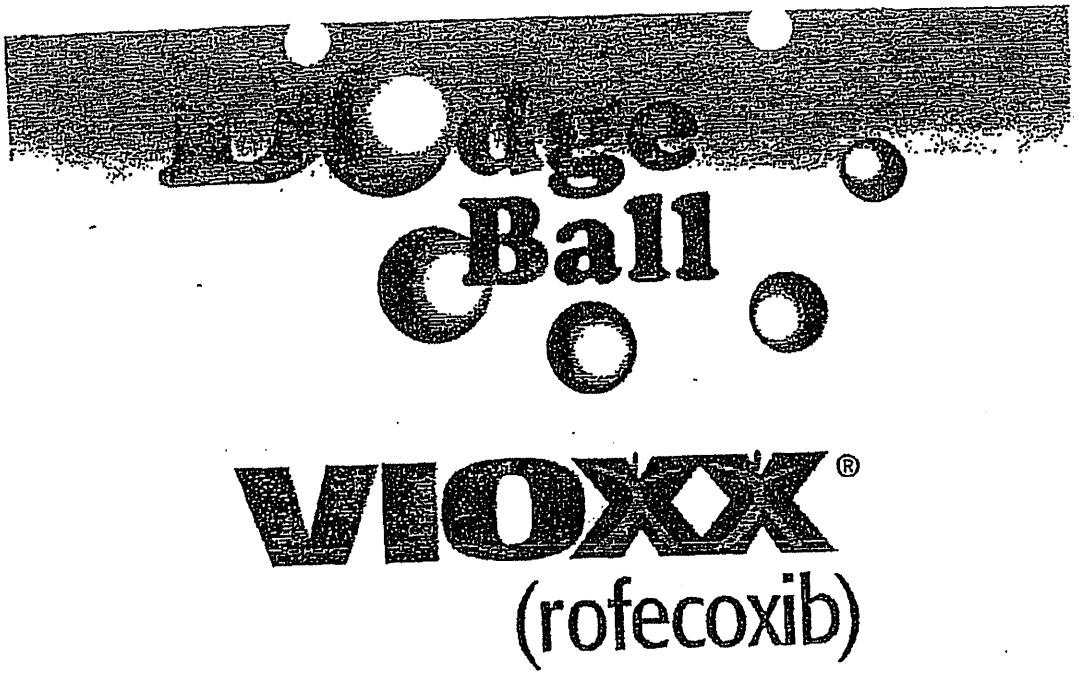
OF COUNSEL:
BEASLEY, ALLEN, CROW, METHVIN,
PORTIS & MILES, P.C.
Post Office Box 4160
Montgomery, Alabama 36103-4160
Phone (334) 269-2343
Fax (334) 223-1236

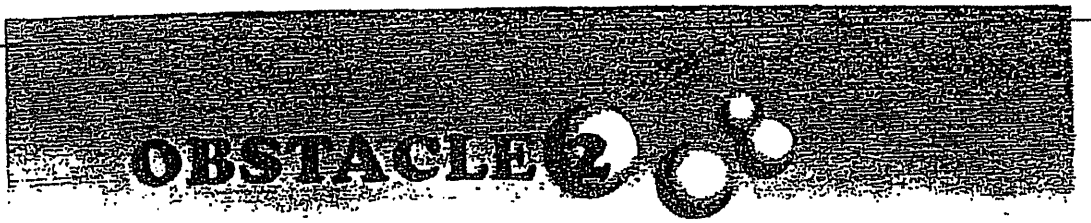
CERTIFICATE OF SERVICE

I hereby certify that I have filed a copy of the foregoing document with the Circuit Clerk along with the Summons and Complaint on this the 10 day of August, 2005.

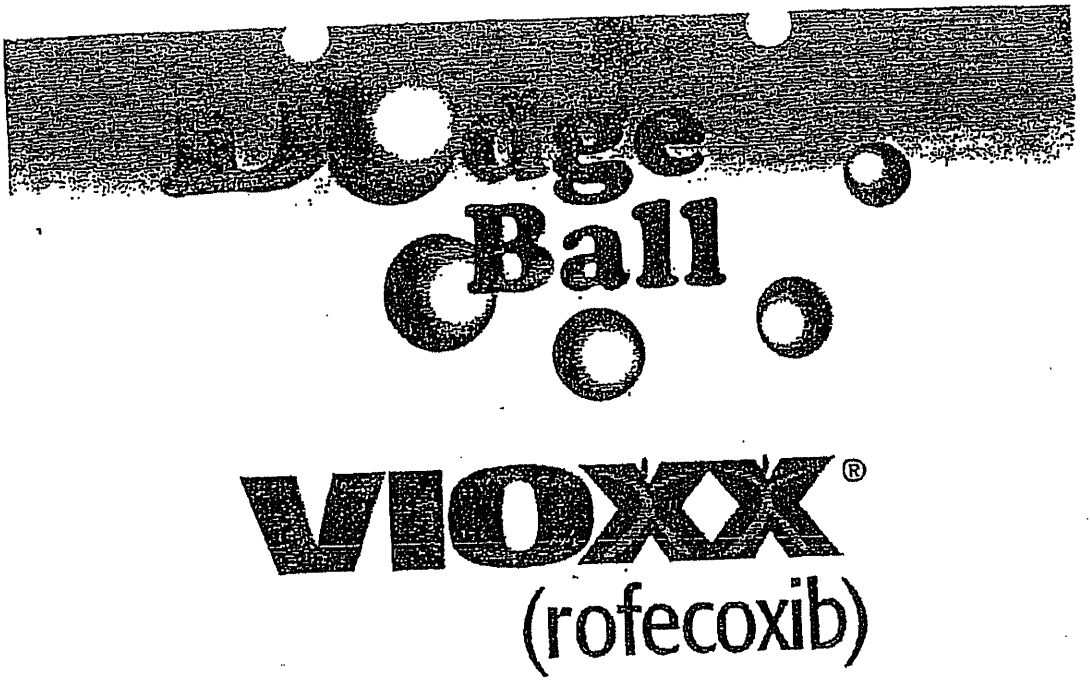


"I am concerned with the potential edema that occurs with Vioxx."





"I am concerned with dose-related increases in hypertension with Vioxx."



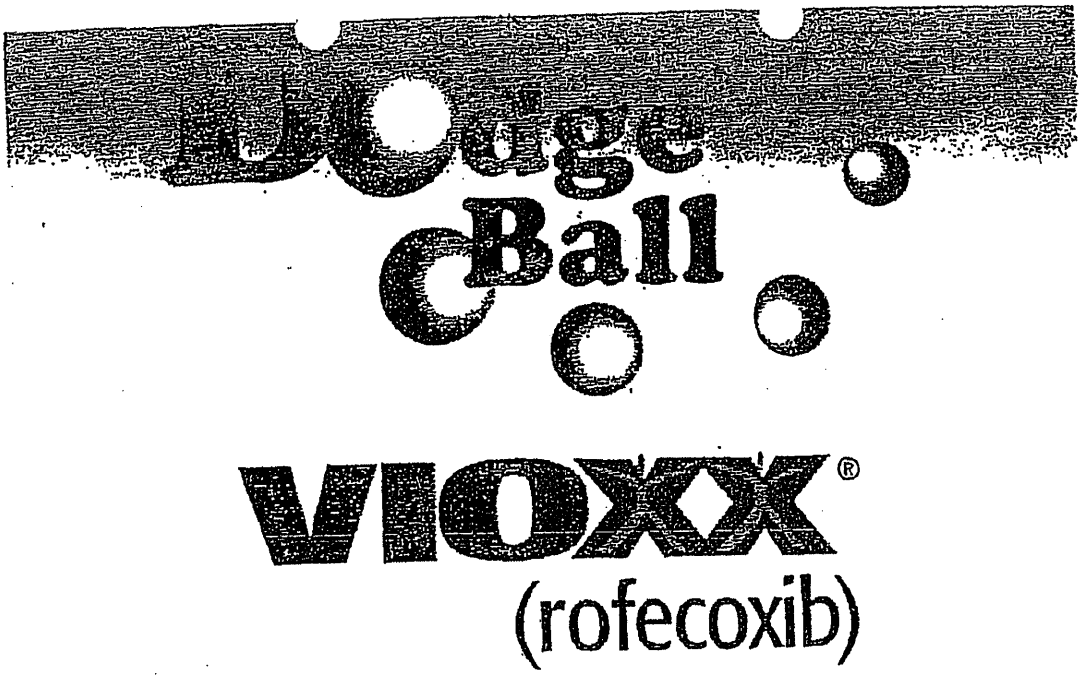
"Can Vioxx be used in patients using low dose aspirin?"

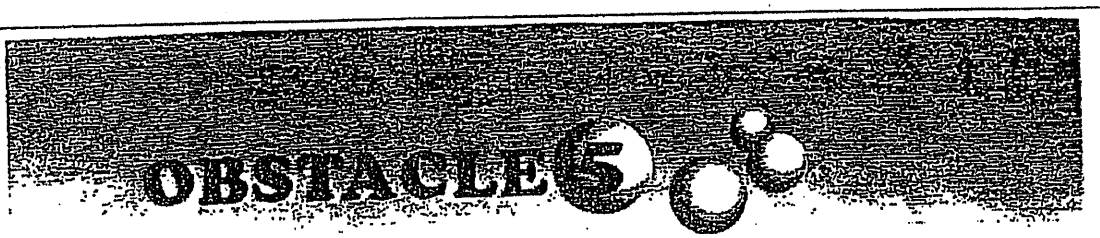
Dodge Ball

VIOXX® (rofecoxib)

OBSTACLE 4

"I am concerned about the cardiovascular effects of Vioxx?"





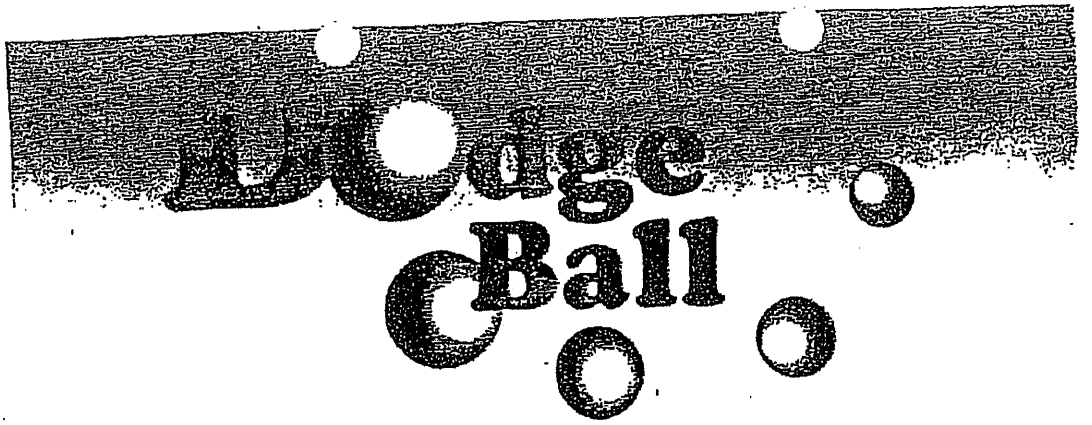
"The competition has been in my office telling me that the incidence of heart attacks is greater with Vioxx than Celebrex."

Dodge Ball

VIOXX® (rofecoxib)

OBSTACLE 6

"There is no difference between Vioxx and Celebrex, why should I use Vioxx?"



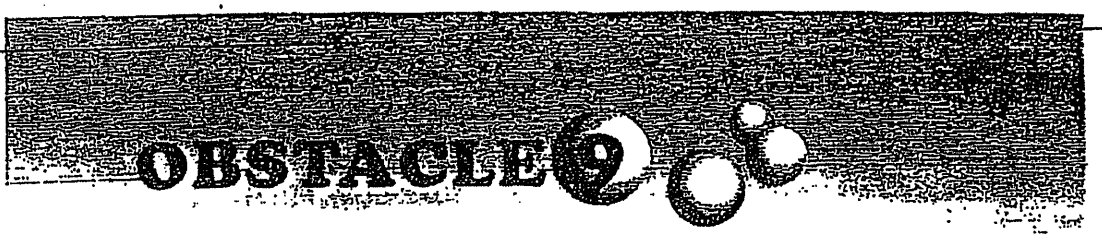
VIOXX®
(rofecoxib)

"Vioxx cannot be used for longer than five days when treating patients for acute pain?"

VIOXX®
(rofecoxib)

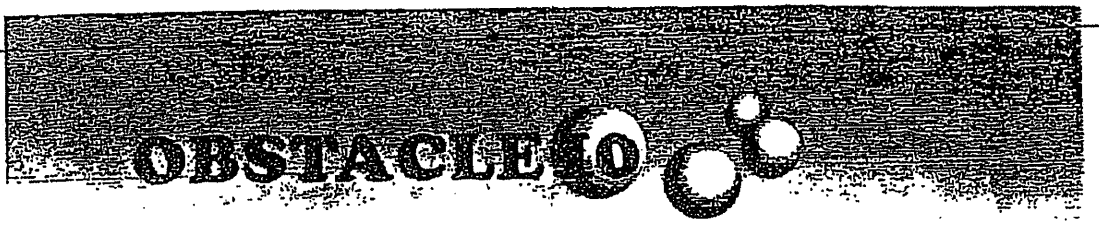
"I use Celebrex. I'm concerned about the safety profile with Vioxx?"

VIOXX®
(rofecoxib)

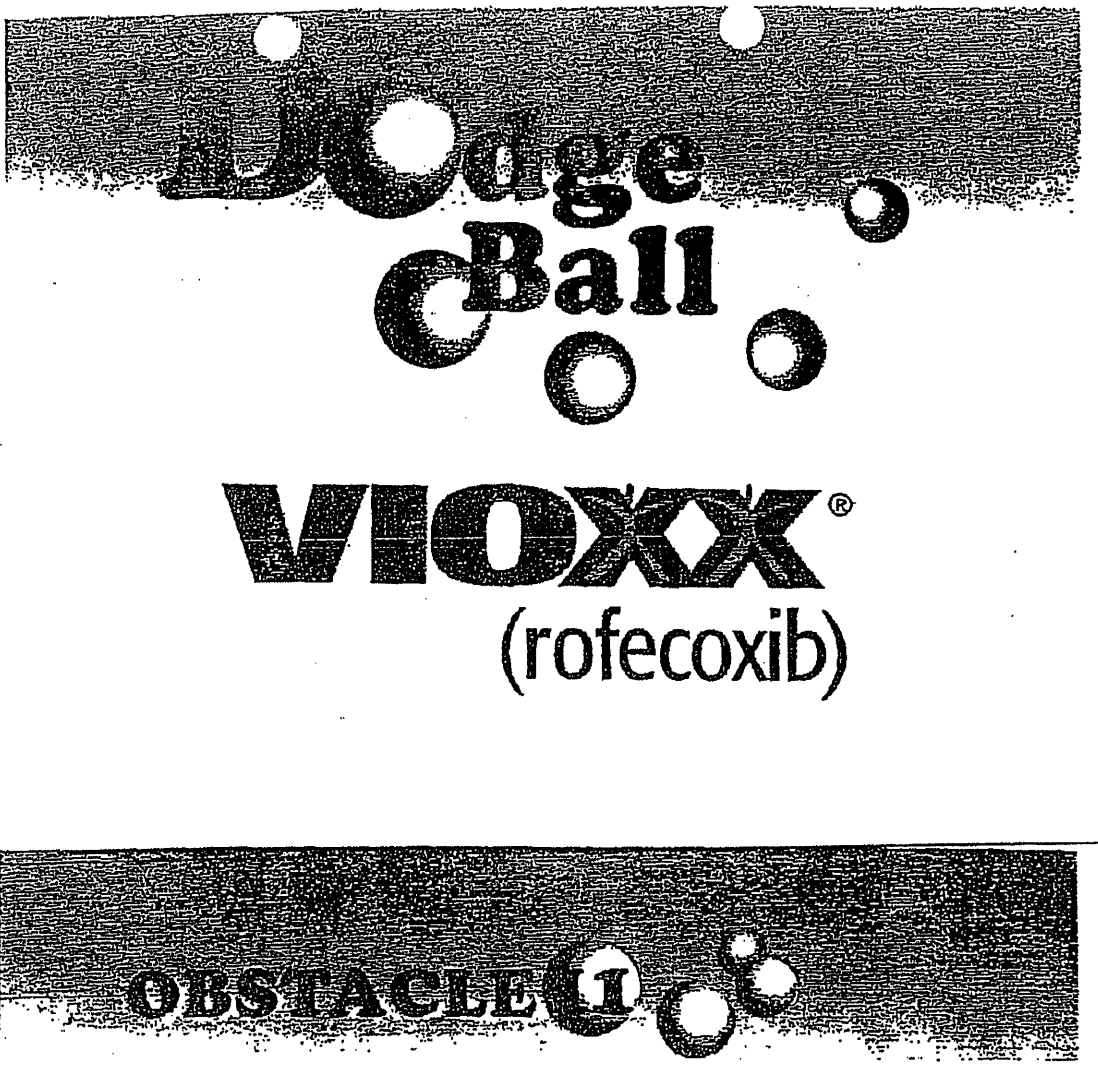


"I understand the new COXIB, Mobic, was just approved."

VIOXX®
(rofecoxib)



"Searle/Pfizer just presented me with data which showed Celebrex 800 mg daily did not exhibit dose dependent increases in side effects compared to the OA and RA doses, and that Vioxx exhibited dose dependent increases in side effects with the 50 mg dose."



OBSTACLE 1

"The new narcotic data looks great, now I'll use Vioxx for all my acute pain patients."

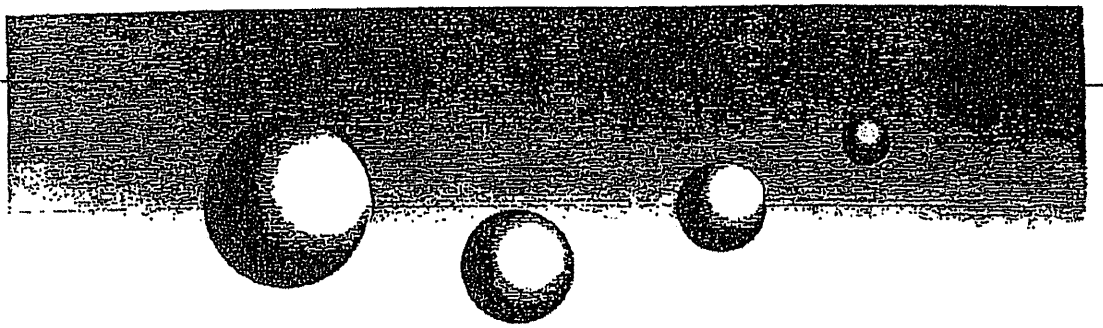
Dodge Ball

VIOXX®
(rofecoxib)

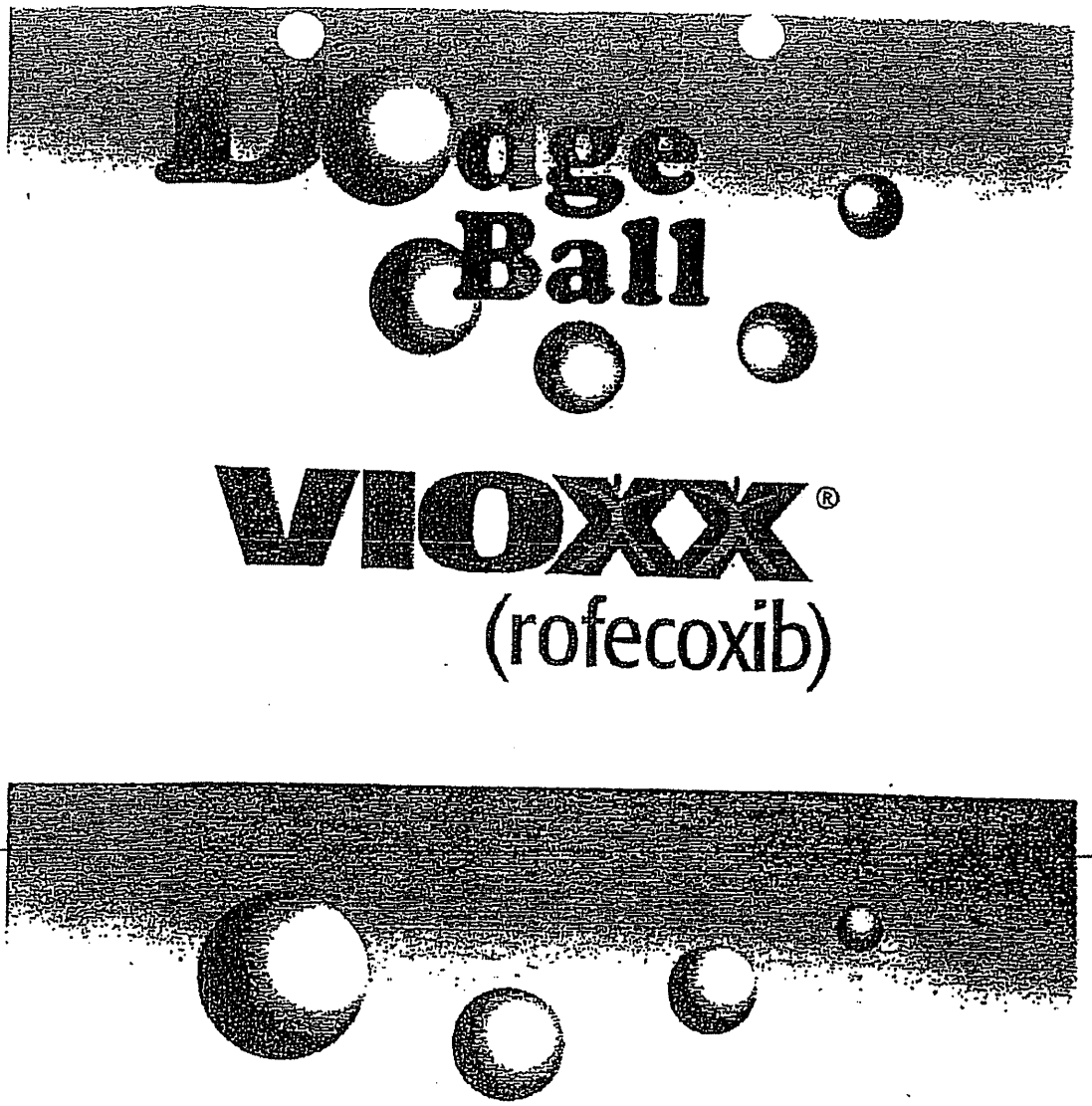
OBSTACLE 2

"I can't use Vioxx because the HMO's require the patients to be on generic NSAIDS first."

VIOXX®
(rofecoxib)



DODGE!



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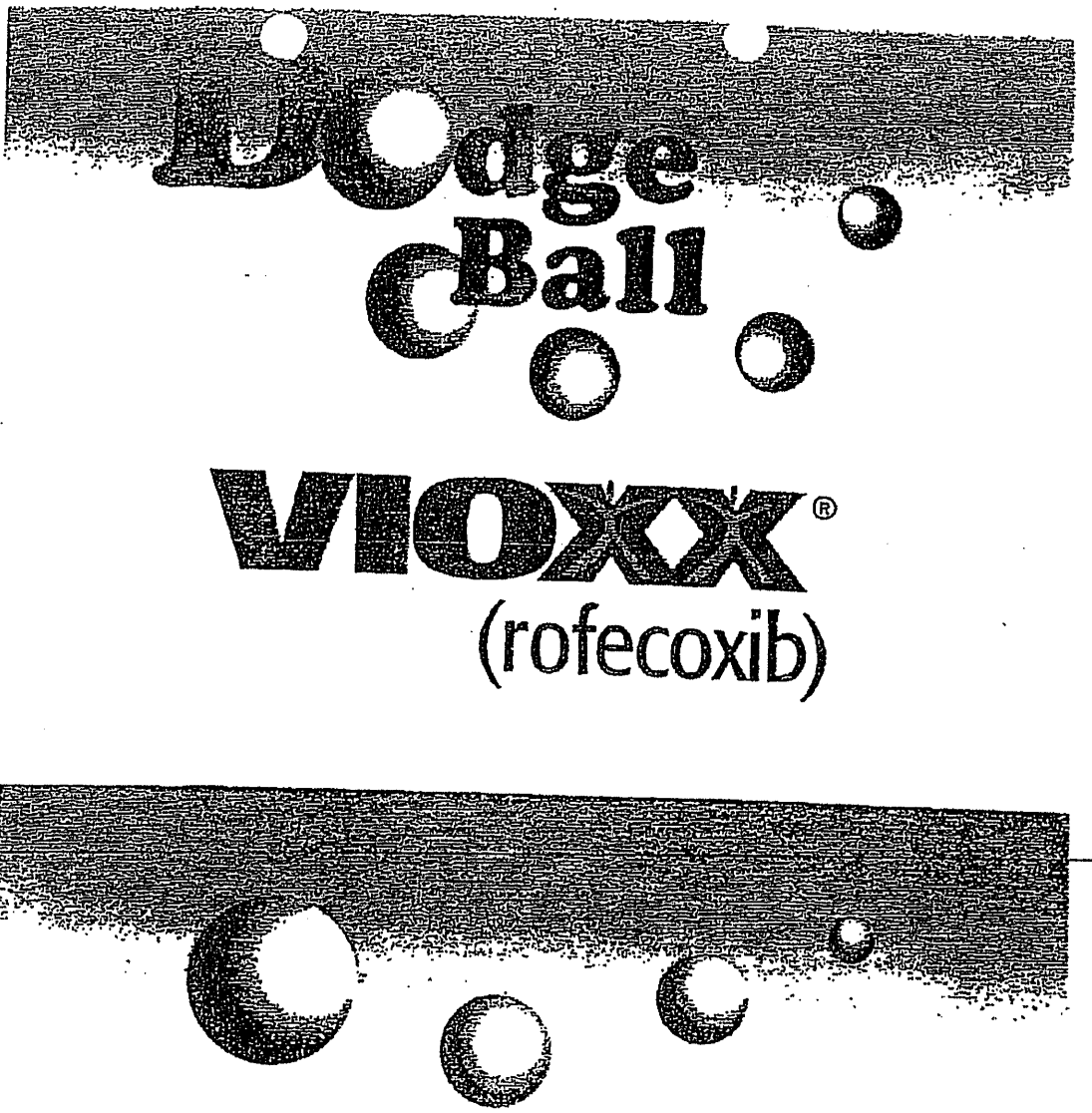
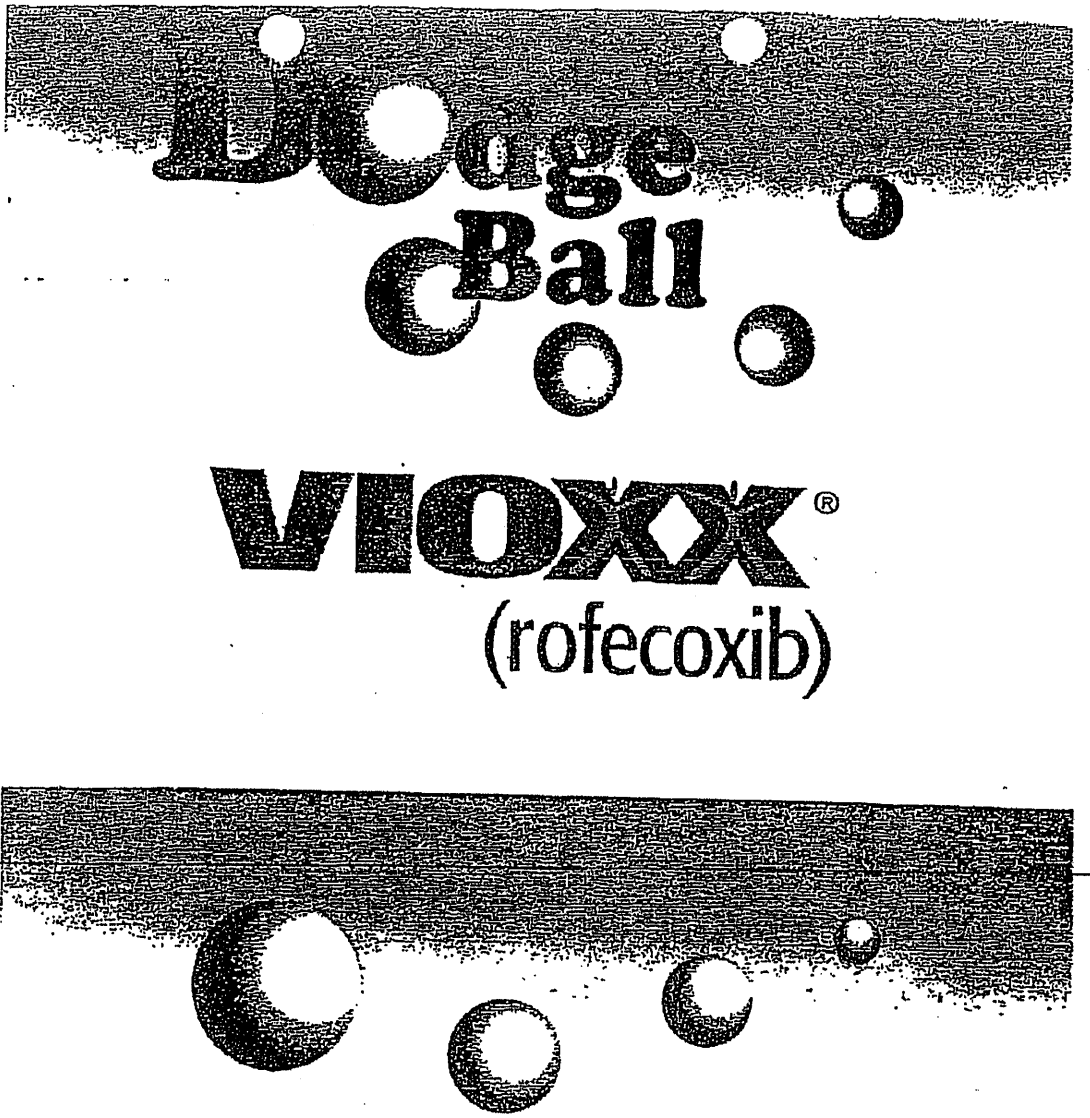




DODGE!

OBSTACLE RESPONSE GUIDE VIOXX®

INFLAMMATORY MANAGEMENT BULLETIN: OBSTACLE RESPONSE GUIDE

TO:
Field Sales Team for VIOXX®

PURPOSE:
To provide you with the initial Obstacle Response Guide. Over time we will be providing you updates and modifications to this resource.

CONTENT:
You are all aware of the process identified for resolving obstacles:

- Pause
- Clarify the Question
- Verify your Understanding of the Issue
- Resolve & Return to the Core Messages

Let's take just a moment to focus on the clarification of the issue. As we launch VIOXX®, we have entered into a very competitive marketplace. Our competition has been aggressively "pre-positioning" our product. This is likely to generate obstacles or issues that need to be resolved before some customers are comfortable prescribing the product for appropriate patients. It will be critical that we clarify the issue prior to attempting to resolve. Many times, the customer may be vague in their statement, such as "I understand VIOXX® has some safety concerns at higher doses." Statements like this could apply to three different issues, methotrexate, warfarin or edema. Unless you clarify, you might respond regarding edema when the physicians concern was warfarin. This approach would actually result in you creating an additional obstacle for yourself.

Some customers may be hesitant to state their true concerns and will use obstacles as a "smokescreen". They hope to distract or redirect you in an attempt to end a product discussion. Again, clarification will be critical. One honest obstacle effectively handled is a tremendous opportunity. Obstacles should be viewed as selling opportunities. Essentially the customer is saying, "I would prescribe if only I knew....." and when you resolve this question, you have earned the right to ask for appropriate patients.

A few final quotes regarding obstacles and the obstacle handling step in selling:

"Obstacles are those frightful things you see when you take your eyes off your goals" – *Unknown*

"The difference between the right words and the almost right words, is the difference between a lightening bolt and a lightening bug." – *Mark Twain*

"Wise people take the complicated and make it simple and understandable." – *Einstein*

"No problem can stand the assault of sustained thinking." – *Voltaire*

"Chance favors the prepared mind." – *Louis Pasteur*

Remember the final step in effective obstacle resolution is to return to the core selling messages of the product. As you review this Obstacle Response Guide, take time to practice both resolving the issue, transition back to your messages and closing the call.

ACTION REQUIRED:
We will be counting on you for two important steps in this process:

1. Identify the issues you are encountering on territory that require a response
2. Effectively implement the responses to resolve the concerns expressed by your customers.

Good Luck and GOOD SELLING!

Obstacles / Responses

1. "There is no difference between VIOXX® and Celebrex. Why should I use VIOXX®?"

Clarify: Doctor, while they both work by inhibiting COX-2, I would like to point out some key clinical areas of distinction that may be important to you and your patients.

INDICATIONS

Once daily VIOXX® is indicated for the relief of the signs and symptoms of OA, management of acute pain in adults and treatment of primary dysmenorrhea, representing all of the indications that were submitted to the FDA for approval of VIOXX®.

Celecoxib is indicated for the signs and symptoms of OA and RA.

Reference:

A&A Training Program ⇒ Module 5 (NSAIDs)
VIOXX® PI ⇒ Indications and Usage (V22)
Celecoxib PI ⇒ Indications and Usage (C23)

CONTRAINDICATIONS

Both VIOXX® and celecoxib are contraindicated in patients who are allergic to them, aspirin or other NSAIDs. Once daily VIOXX® is not contraindicated in patients with sulfonamide allergies, commonly known as sulfa allergies.

In contrast, celecoxib is contraindicated in patients with allergic-type reactions to sulfonamides. This contraindication is unique to celecoxib, due to its molecular structure, and is **not a class effect**. Sulfonamide allergies are common drug allergies in the US population and allergic reactions can range from mild to more serious.

Once daily VIOXX® offers simplicity - simplified prescribing without having to worry about a sulfonamide allergy contraindication.

Reference:
VIOXX® PI ⇒ Contraindication (V23)
Celecoxib PI ⇒ Contraindication (C24)

DOSING

Doctor, VIOXX® offers dosing simplicity of once daily dosing for all indications – the relief of the signs and symptoms of OA, management of acute pain in adults, and the treatment of primary dysmenorrhea. With celecoxib, each time you see an OA patient you must decide whether to prescribe it once a day or twice a day. VIOXX® also offers the option to increase the dose to 25 mg once daily for OA patients who need additional relief. Celecoxib has one dose – 200 mg, and its label states that no additional efficacy is seen with 200 mg BID.

Reference:
VIOXX® PI ⇒ Dosage and Administration ⇒ Osteoarthritis (V65) and Management of Acute Pain and Treatment of Primary Dysmenorrhea (V66)
Celecoxib PI ⇒ Dosage and Administration ⇒ Osteoarthritis (C54)

METABOLISM

Once daily VIOXX® is metabolized primarily through cytosolic enzymes in the liver. Unlike once daily VIOXX®, celecoxib is metabolized through the cytochrome P450 system.

(Remember to provide appropriate balancing information on use in hepatic insufficiency and hepatic effects.)

Reference:
VIOXX® PI ⇒ Clinical Pharmacology ⇒ Pharmacokinetics ⇒ Metabolism (V7)

COMPREHENSIVE CLINICAL STUDIES

Once daily VIOXX® has been comprehensively studied. In OA patients, once daily VIOXX® was compared to diclofenac in two 1-year studies. The endoscopy studies were six-month studies. We have data on serious upper GI events out to one year. This was the most comprehensive clinical program ever run by Merck. Let me share some of the data with you...

Transition to strength, safety and simplicity messages.

Reference:
VIOXX® PI ⇒ Clinical Studies ⇒ OA (V16)

2. "I can't use VIOXX® with patients being treated with methotrexate."

Doctor, once daily VIOXX® is not contraindicated in patients receiving methotrexate. No dosage adjustments of once daily VIOXX® and no change in the standard monitoring for methotrexate are required for patients taking methotrexate with once daily VIOXX®.

If probed further:
Doctor, according to the product circular for once daily VIOXX®, at doses of 75 mg (which is 3 to 6 times the OA therapeutic dose), once daily VIOXX® increased plasma concentrations of methotrexate by 23%. At 24 hours post dose or at the trough period, a similar proportion of patients receiving VIOXX® or placebo had methotrexate plasma concentrations below the measurable limit. According to the methotrexate label, methotrexate-toxicity is believed to be more dependent on time of exposure rather than peak levels. Again doctor, no dosage adjustments of once daily VIOXX® and no change in the standard monitoring for methotrexate are required for patients taking methotrexate with once daily VIOXX®.

Transition to strength, safety and simplicity messages.

Reference:
VIOXX® PI ⇒ Precautions ⇒ Drug Interactions ⇒ Methotrexate (V47)

3. "Is VIOXX® contraindicated in patients being treated with warfarin?"

No. Once daily VIOXX® is not contraindicated in patients taking warfarin and no change in standard monitoring is required. According to the package insert, when therapy with once daily VIOXX® is initiated or changed, patients should be monitored for INR* values. Doctor, the recommendation for once daily VIOXX® is the same recommendation for warfarin when any new therapy is initiated.

Transition to strength, safety and simplicity messages.

If further probed, refer to the PI:
In a 21-day multiple-dose study in healthy individuals stabilized on warfarin (2 to 8.5 mg daily), administration of VIOXX® 25 mg QD was associated with mean increases in INR* of approximately 8% (range of INR on warfarin alone, 1.1 to 2.2; range of INR on warfarin plus VIOXX®, 1.2 to 2.4). Somewhat greater mean increases in INR of ~11% (range of maximum INR on warfarin alone, 1.5 to 2.7; range of maximum INR on warfarin plus VIOXX®, 1.6 to 4.4) were also seen in a single dose PK screening study using a 30-mg dose of warfarin and 50 mg of VIOXX®. Standard monitoring of INR values should be conducted when therapy with VIOXX® is initiated or changed, particularly in the first few days, in patients receiving warfarin or similar agents.

(Submit a PIR if appropriate.)

Transition to strength, safety and simplicity messages.

Reference:
VIOXX® PI ⇒ Precautions ⇒ Drug Interactions ⇒ Warfarin (V51)

***INR** – International Normalized Ratios. This is a standardized way of measuring the degree of anti-coagulation produced by warfarin.

4. "I'm concerned about the potential edema that occurs with VIOXX®."

Clarify:
What are your specific concerns regarding edema?

If the physician's concern is the overall incidence of edema with once daily VIOXX®, then respond:
Doctor, edema is reported with all NSAIDs and is thought to result from cyclooxygenase inhibition in the kidney. Clinical trials with once daily VIOXX® 12.5 and 25 mg have shown renal effects such as edema similar to those observed with comparator NSAIDs. In these studies, the incidence rates for lower extremity edema were as follows: (In the AE table, point to row on edema under Body As A Whole)

VIOXX® 12.5 mg or 25 mg once daily - 3.7%
Ibuprofen 2400 mg – 3.8%
Diclofenac 150 mg –3.4%
Placebo – 1.1%

In clinical trials, the effects of edema were mild and there were no discontinuations due to edema.

If the physician's concern is the dose related increase of edema with once daily VIOXX® 50 mg, then respond:

Doctor, let me explain where the use of 50 mg is recommended. 50 mg is recommended for use in acute pain in adults. It has been studied for up to 5 days. In these studies, the renal effects of once daily VIOXX®– such as edema – were generally similar to comparator NSAIDs.

The 50 mg dose is not recommended for OA. However, in clinical trials with once daily VIOXX® 50 mg up to 6 months, there was a higher incidence of lower extremity edema.

Finally, let me point out that edema is reported with all NSAIDs and is thought to result from cyclooxygenase inhibition (COX-2) in the kidney.

Transition to strength, safety and simplicity messages.

Reference:
VIOXX® PI ⇒ Adverse Reactions ⇒ OA ⇒ Table and second paragraph (V59)
VIOXX® PI ⇒ Precautions ⇒ Fluid Retention and Edema (V35)

5. "It is my understanding that VIOXX® was denied an indication for RA by the FDA."

Clarify: Doctor, what is your true concern?

If physician mentions denial of an RA indication, respond:
Doctor, Merck was not denied any indications. Once daily VIOXX® is indicated for relief of the signs and symptoms of OA, management of acute pain in adults, and for the treatment of primary dysmenorrhea. These represent all of the indications that Merck submitted to the FDA for the approval of once daily VIOXX®.

If appropriate, state: Last month when I was in, you stated that the majority of your arthritis patients suffer from OA. I would like for us to discuss how once daily VIOXX® could benefit these patients.

Transition to strength, safety and simplicity messages.

(After close: If you need information on the use of VIOXX® in RA, I can submit a PIR.)

If the physician is concerned about the anti-inflammatory effect, see obstacle #6.

Reference:
VIOXX® PI ⇒ Indications and Usage (V22)
VIOXX® PI ⇒ Clinical Pharmacology ⇒ Mechanism of Action (V3)

6. "VIOXX® is not an anti-inflammatory drug."

Doctor, the Mechanism of Action section of the package insert for once daily VIOXX® clearly states: "VIOXX® is a nonsteroidal anti-inflammatory drug that exhibits anti-inflammatory, analgesic, and anti-pyretic activities in animal models." Once daily VIOXX® 12.5 and 25 mg reduced the signs and symptoms of OA as effectively as 2400 mg of ibuprofen. Also, once daily VIOXX® produced significant reductions in joint stiffness upon first awakening in the morning. Doctor, as you know, morning stiffness is one indicator of inflammation.

In addition, let me point out that in the label it also states "because of the anti-inflammatory effects of VIOXX®, the pharmacological activity of VIOXX® in reducing inflammation, and possibly fever, may diminish the utility of these diagnostic signs in detecting infectious complications of presumed noninfectious, painful conditions."

Doctor, would you agree that once daily VIOXX® has anti-inflammatory effects?

Transition to strength, safety and simplicity messages.

Reference:
VIOXX® PI ⇒ Clinical Pharmacology ⇒ Mechanism of Action (V3)
VIOXX® PI ⇒ Clinical Studies ⇒ OA (V16)
VIOXX® PI ⇒ Precautions ⇒ General (V31)

7. "Can VIOXX® be used in patients using low dose aspirin?"

Let me share with you the experience we have on the concomitant use of once daily VIOXX® and low-dose aspirin. At steady state, once daily VIOXX® 50 mg had no effect on the anti-platelet activity of low-dose (81 mg once daily) aspirin.

I should also remind you that once daily VIOXX® is not a substitute for aspirin for cardiovascular prophylaxis and that concomitant administration of low-dose aspirin with once daily VIOXX® may result in an increased risk of GI ulceration or other complications compared with use of once daily VIOXX® alone.

Transition to strength, safety and simplicity messages.

Reference:
VIOXX® PI ⇒ Precautions ⇒ Drug Interactions ⇒ Aspirin (V41)

8. "I understand that VIOXX® has sulfur as part of its chemical structure. Is it contraindicated for patients with "sulfa allergies?"

No. Doctor, let me show you the contraindications section of the label. Once daily VIOXX® is not contraindicated for patients with known sulfonamide allergies, commonly known as "sulfa allergies."

Unlike once daily VIOXX®, celecoxib is contraindicated in patients with sulfonamide allergies. Celecoxib contains a sulfonamide group ($S\text{-}NH_2$), which is associated with sulfa allergies. This contraindication is based on the specific chemical structure of celecoxib and is not a class effect. Sulfonamide allergies are common drug allergies in the US population and allergic reactions can range from mild to more serious.

Once daily VIOXX® offers simplicity, with no sulfonamide allergy contraindication.

~~Transition to strength, safety and simplicity messages.~~

Reference:
VIOXX® PI ⇒ Contraindications (V23)

9. "Why wasn't VIOXX® 50 mg studied for longer than five days in acute pain?"

To obtain an indication for the management of acute pain in adults, all analgesic drugs are studied in short-term standard pain models as defined by the FDA. The maximum time for these studies for once daily VIOXX® was 5 days. However, let me point out that while it is not a recommended dose for OA, once daily VIOXX® 50 mg was studied out to 6 months. In these studies, the general safety profile of once daily VIOXX® 50 mg was similar to the recommended doses, except for a higher incidence of GI symptoms, lower extremity edema, and hypertension. Also, let me point out that once daily VIOXX® is indicated for the treatment of acute pain. The studies that support this acute pain indication lasted up to 5 days. But as I mentioned, while it is not a recommended OA dose, once daily VIOXX® 50 mg was studied for up to 6 months in OA patients – so the profile is well defined in the circular.

~~If further probed: "But, I'm worried about GI safety long-term."~~
Doctor, in two identical studies of OA patients receiving once daily VIOXX® 25 or 50 mg for up to 24 weeks, once daily VIOXX® demonstrated significantly fewer endoscopic ulcers than ibuprofen.

Once daily VIOXX® also has GI event data from clinical trials up to one year. Among 3,357 patients who were treated with once daily VIOXX® 12.5, 25, and 50 mg in controlled clinical trials of 6-weeks to 1 year, a total number of four patients experienced a serious upper GI event. Two patients experienced an upper GI bleed within 3 months (0.06%); one experienced an obstruction within 6 months; and one experienced an upper GI bleed within 12 months, for a total incidence of 0.12% over 1 year.

Transition to strength, safety and simplicity messages.

Reference:
VIOXX® PI ⇒ Clinical Studies ⇒ Analgesic Studies (V17)
VIOXX® PI ⇒ Clinical Studies ⇒ OA (V16)

10. "Why didn't you compare VIOXX® to higher doses of ibuprofen or naproxen sodium for the management of pain?"

To obtain an indication for the management of acute pain in adults, a drug must be studied in standard pain models as defined by the FDA. As it states in the ibuprofen PI, in clinical studies using doses of ibuprofen greater than 400mg are no more effective than the 400mg dose in analgesia. Also, the maximum recommended dose of naproxen for analgesia is 550 mg.

In acute analgesic models of post-orthopedic surgical pain, post-operative dental pain and primary dysmenorrhea, once daily VIOXX® relieved pain that was rated by patients as moderate to severe. In post-surgical dental pain studies, the onset of action with a single 50mg dose of once daily VIOXX® occurred within 45 minutes.

Transition to strength, safety and simplicity messages.

Reference:

VIOXX® PI ⇒ Clinical Studies ⇒ Analgesia (V17)

11. "When do I prescribe VIOXX® 12.5 mg, 25 mg, or 50 mg once daily?"

Whether you're treating OA or acute pain, once daily VIOXX® is always a simple once daily dose.

12.5 mg or 25 mg once daily for OA

Once daily VIOXX® 12.5mg is the starting dose for OA. If a patient requires greater pain relief, you have the flexibility to increase the dose to 25mg once daily at no additional cost to the patient.

50 mg once daily for Acute Pain and Primary Dysmenorrhea

In patients with moderate to severe acute pain, the dose is 50mg once daily. Once daily VIOXX® relieved moderate to severe pain following orthopedic surgery, dental surgery and primary dysmenorrhea.

In addition to the simplicity of once daily dosing, once daily VIOXX® also adds the flexibility of oral suspension for both strengths.

Transition to strength, safety and simplicity messages:

Reference:
VIOXX® PI ⇒ Dosage and Administration (V65-V67)

12. "Can I use VIOXX® in patients with renal impairment?"

No dosage adjustment is recommended for patients with mild to moderate renal impairment. Use of once daily VIOXX® in patients with advanced renal disease is not recommended because no safety information is available regarding the use of once daily VIOXX® in these patients.

Transition to strength, safety and simplicity messages.

Reference:
VIOXX® PI ⇒ Precautions ⇒ Renal Effects (V33)
VIOXX® PI ⇒ Precautions ⇒ Fluid Retention and Edema (V35)

13. "Why doesn't VIOXX® have a 50 mg tablet?"

Once daily VIOXX® is not offered in a single 50 mg tablet and a dosage of 50mg can be easily achieved by taking two 25 mg tablets.

Transition to strength, safety and simplicity messages.

Reference:
VIOXX® PI ⇒ Dosage and Administration (V66)

14. "How does your price compare to Celebrex and other branded NSAIDs?"

Doctor, the catalog price for once daily VIOXX® is $2.02 for both 12.5 mg and 25 mg, offering your patients one of the best values available.

The catalog price for celecoxib is $2.38 for 100mg bid and $2.02 for 200 mg qd.

In addition, the catalog price for the oral suspension of once daily VIOXX® is competitive with other NSAIDs at $3.00.

This price comparison does not establish that products have comparable efficacy. These prices reflect direct cost and do not reflect actual costs paid by consumers.

Transition to strength, safety and simplicity messages.

(For your reference, the average wholesale price (AWP) for once daily VIOXX® is $2.42 for both 12.5 mg and 25 mg. AWP for celecoxib is $2.86 for 100 mg BID and $2.42 for 200 mg qd. AWP for the oral suspension of once daily VIOXX® is competitive with other NSAIDs at $3.60.)

15. "Isn't a 17-hour half-life inconsistent with once daily dosing?"

The 17 hour half-life of once daily VIOXX® is entirely consistent with its once daily dosing. In all OA studies, lasting from 6 to 86 weeks with 3900 patients, once daily treatment with VIOXX® 12.5 and 25 mg in the morning was associated with a significant reduction in joint stiffness upon first awakening in the morning. At doses of 12.5 and 25 mg once daily, the effectiveness of once daily VIOXX® was shown to be comparable to ibuprofen 800mg TID and diclofenac 50 mg TID.

If probed further on half life:
Doctor, many drugs with half-lives shorter than 24 hour are effective when dosed once a day, for example Singulair, Prinivil, and Zocor.

Transition to strength, safety and simplicity messages.

Reference:

VIOXX® PI ⇒ Clinical Pharmacology ⇒ Excretion (V8)
VIOXX® PI ⇒ Clinical Studies ⇒ OA (V16)
SINGULAIR® PI ⇒ Clinical Pharmacology ⇒ Excretion
PRINIVIL® PI ⇒ Clinical Pharmacology ⇒ Excretion
ZOCOR® PI ⇒ Clinical Pharmacology ⇒ Excretion

MERCK

MEMO

TO: All Field Personnel with Responsibility for VIOXX

FROM: Market Integration Team for VIOXX

SUBJECT: Top Ten Obstacle Handlers

Enclosed is the complete Obstacle Handling Guide for VIOXX. This Guide includes all obstacle responses issued since the launch of VIOXX. Though it is important for you to be familiar with all of the obstacle handlers, the following Top Ten Obstacle Handlers are the most important obstacle handlers at this time as they center around current issues in the field.

Cardiovascular Events

Obstacle Response #7- "Can VIOXX be used in patients using low dose aspirin?"

Obstacle Response #23- "I am concerned about the cardiovascular effects of VIOXX."

Obstacle Response #38- "The competition has been in my office telling me that the incidence of heart attacks (or cardiovascular events) is greater with VIOXX than Celebrex." OR "I just read (or heard) a news story stating that VIOXX has a higher incidence of heart attacks than Celebrex."

Renal Effects

Obstacle Response #4- "I am concerned about the potential edema that occurs with VIOXX."

Obstacle Response #20- "Can I use VIOXX with Ace Inhibitors?"

Obstacle Response #31- "I am concerned about dose-related increases in hypertension with VIOXX."

VIOXX 50mg Tablet

Obstacle Responses #9 and 9a- "Why wasn't VIOXX 50mg studied for longer than five days in acute pain?" OR "VIOXX cannot be used for longer than five days when treating patients for acute pain."

Obstacle Response #30- "Searle/Pfizer just presented me with new data which showed that Celebrex 800mg daily did not exhibit dose dependent increases in side effects compared to the OA and RA doses, and that VIOXX exhibited dose dependent increases in side effects with the 50mg dose."

General

Obstacle Response #26- "I use Celebrex. I'm concerned about the safety profile of VIOXX."

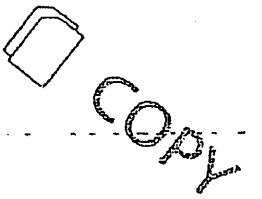
Obstacle Response #34- "I understand the new COX-2 agent, MOBIC, was just approved."

EXHIBIT "C"

COPY

OBSTACLE RESPONSE GUIDE VIOXX

Obstacle Response Guide



List of Obstacles

1. "There is no difference between VIOXX and Celebrex. Why should I use VIOXX?"

2. "I can't use VIOXX with patients being treated with methotrexate."

3. "Is VIOXX contraindicated in patients being treated with warfarin?"

3a. I received this letter from Searle about Celebrex and warfarin. What can you tell me about it and VIOXX?

4. "I'm concerned about the potential edema that occurs with VIOXX."

5. "It is my understanding that VIOXX was denied an indication for RA by the FDA."

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6. "VIOXX is not an anti-inflammatory drug."

7. "Can VIOXX be used in patients using low dose aspirin?"

8. "I understand that VIOXX has sulfur as part of its chemical structure. Is it contraindicated for patients with "sulfa allergies?"

9. "Why wasn't VIOXX 50 mg studied for longer than five days in acute pain?"

9a. "VIOXX cannot be used for longer than five days when treating patients for acute pain"

10. "Why didn't you compare VIOXX to higher doses of ibuprofen or naproxen sodium for the management of pain?"

11. "When do I prescribe VIOXX 12.5 mg, 25 mg, or 50 mg once daily?"

12. "Can I use VIOXX in patients with renal impairment?"

13. "Why doesn't VIOXX have a 50 mg tablet?" DELETED

14. "How does your price compare to Celebrex and other branded NSAIDs?"

15. "Isn't a 17-hour half-life inconsistent with once daily dosing?"

16. "Since VIOXX is not primarily metabolized by the cytochrome P450 system and that is a benefit for VIOXX, should I be concerned about the fact that COZAAR is metabolized by the P450 system?"

    or

    "How is the CYP450 issue with Celebrex any different from COZAAR?"

17. "Since VIOXX is not primarily metabolized by the cytochrome P450 system and that is a benefit for VIOXX, should I be concerned about the fact that ZOCOR is metabolized by the P450 system?"

    or

    "How is the CYP450 issue with Celebrex any different from ZOCOR?"

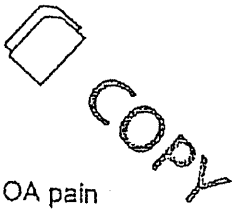
18. "The pain studies for VIOXX were not well designed."

19. "What hepatic effects can I expect with VIOXX?"

20. "Can I use VIOXX with ACE inhibitors?"

21. "VIOXX is only comparable to a single dose of naproxen."

22. "I've been told that 45% of VIOXX is metabolized through the cytochrome P450 system."



23. "I am concerned about the cardiovascular effects of VIOXX."

24. "Your PI states that VIOXX provided a significant reduction in OA pain after one to two weeks. Why should I use VIOXX when Celebrex states OA patients achieved significant reduction in pain within 24-48 hours after initiation of dosing?"

25. "Do I have to discontinue VIOXX pre or post-operatively?"

26. "I use Celebrex. I'm concerned about the safety profile of VIOXX. (Cumulative vs. Additive clarification)

27. "Why are you telling me not to prescribe Celebrex for sulfa-allergic patients when Hyzaar has the same contraindication?"

28. "The two recent JAMA articles showed that Celebrex provided greater reductions in events than VIOXX." OR "It looks like there are still a lot of PUB's in the VIOXX group; why is the reduction only 50% and not 100%?"

29. "I understand Celebrex just received an FDA approval for prevention of cancer. Is VIOXX receiving a similar indication soon?"

30. "Searle/Pfizer just presented me with new data which showed that Celebrex 800mg daily did not exhibit dose dependent increases in side effects compared to the OA and RA doses, and that VIOXX exhibited dose dependent increases in side effects with the 50mg dose."

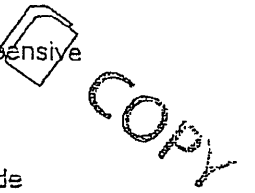
31. "I am concerned with dose-related increases in hypertension with VIOXX."

32. "Celebrex must be a safer agent. Unlike VIOXX, Celebrex outcomes data did not show any increases in myocardial infarctions or stroke."

33. "Why didn't VIOXX report the p-values for its' OUTCOMES STUDY?" DELETED

34. "I understand the new COX-2 agent, Mobic, was just approved."

35. "The Mobic representative told me that Mobic is 20% less expensive than VIOXX. I am considering using Mobic due to the cost advantage."



36. "I am impressed with Mobic's tremendous amount of worldwide experience."

37. "The Mobic representative has shown me data from two large-scale studies, the MELISSA and SELECT trials, which emphasized Mobic's GI tolerability. I find these studies very comprehensive and impressive."

38. " The competition has been in my office telling me that the incidence of heart attacks [or cardiovascular events] is greater with VIOXX than Celebrex."

OR

"I just read [or heard] a news story stating that VIOXX has a higher incidence of heart attacks than Celebrex."

[redacted]

Clarify: Doctor, while they both work by inhibiting COX-2, I would like to point out some key clinical areas of distinction that may be important to you and your patients.

INDICATIONS

Once daily VIOXX is indicated for the relief of the signs and symptoms of OA, management of acute pain in adults and treatment of primary dysmenorrhea, representing all of the indications that were submitted to the FDA for approval of VIOXX.

Celecoxib is indicated for the signs and symptoms of OA and RA.

Reference:
A&A Training Program ⇒ Module 5 (NSAIDs)
VIOXX PI ⇒ Indications and Usage (V22)
Celecoxib PI ⇒ Indications and Usage (C23)

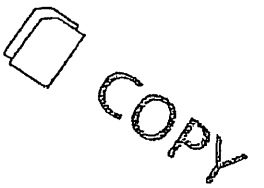
CONTRAINDICATIONS

Both VIOXX and celecoxib are contraindicated in patients who are allergic to them, aspirin or other NSAIDs. Once daily VIOXX is not contraindicated in patients with sulfonamide allergies, commonly known as sulfa allergies.

In contrast, celecoxib is contraindicated in patients with allergic-type reactions to sulfonamides. This contraindication is unique to celecoxib, due to its molecular structure, and is not a class effect. Sulfonamide allergies are common drug allergies in the US population and allergic reactions can range from mild to more serious.

Once daily VIOXX offers simplicity - simplified prescribing without having to worry about a sulfonamide allergy contraindication.

Reference:
VIOXX PI ⇒ Contraindication (V23)
Celecoxib PI ⇒ Contraindication (C24)



DOSING

Doctor, VIOXX offers dosing simplicity of one tablet, once daily dosing for all indications – the relief of the signs and symptoms of OA, management of acute pain in adults, and the treatment of primary dysmenorrhea. With celecoxib, each time you see an OA patient you must decide whether to prescribe it once a day or twice a day. VIOXX also offers the option to increase the dose to 25 mg once daily for OA patients who need additional relief. Celecoxib has one dose – 200 mg, and its label states that no additional efficacy is seen with 200 mg BID.

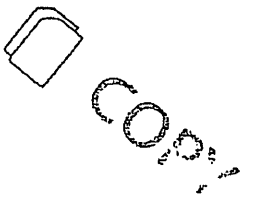
Reference:
VIOXX PI ⇒ Dosage and Administration ⇒ Osteoarthritis (V65) and Management of Acute Pain and Treatment of Primary Dysmenorrhea (V66)
Celecoxib PI ⇒ Dosage and Administration ⇒ Osteoarthritis (C54)

METABOLISM

Once daily VIOXX is metabolized primarily through cytosolic enzymes in the liver. Unlike once daily VIOXX, celecoxib is metabolized through the cytochrome P450 system.

(Remember to provide appropriate balancing information on use in hepatic insufficiency and hepatic effects.)

Reference:
VIOXX PI ⇒ Clinical Pharmacology ⇒ Pharmacokinetics ⇒ Metabolism (V7)



COMPREHENSIVE CLINICAL STUDIES

Once daily VIOXX has been comprehensively studied. In OA patients, once daily VIOXX was compared to diclofenac in two 1-year studies. The endoscopy studies were six-month studies. We have data on serious upper GI events out to one year. This was the most comprehensive clinical program ever run by Merck. Let me share some of the data with you...

VIOXX demonstrated significantly fewer endoscopic ulcers than ibuprofen and was consistent across all studies.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:
VIOXX PI ⇒ Clinical Studies ⇒ OA (V16)

2. If concerns VIOXX with patients being treated with methotrexate

Doctor, once daily VIOXX is not contraindicated in patients receiving methotrexate. No dosage adjustments of once daily VIOXX and no change in the standard monitoring for methotrexate are required for patients taking methotrexate with once daily VIOXX.

If probed further:
Doctor, according to the product circular for once daily VIOXX, at doses of 75 mg (which is 3 to 6 times the OA therapeutic dose), once daily VIOXX increased plasma concentrations of methotrexate by 23%. At 24 hours post dose or at the trough period, a similar proportion of patients receiving VIOXX or placebo had methotrexate plasma concentrations below the measurable limit. According to the methotrexate label, methotrexate-toxicity is believed to be more dependent on time of exposure rather than peak levels. Again doctor, no dosage adjustments of once daily VIOXX and no change in the standard monitoring for methotrexate are required for patients taking methotrexate with once daily VIOXX.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:
VIOXX PI ⇒ Precautions ⇒ Drug Interactions ⇒ Methotrexate (V47)

COPY

[redacted]

No. Once daily VIOXX is not contraindicated in patients taking warfarin. According to the package insert, when therapy with once daily VIOXX is initiated or changed, patients should be monitored for INR* values, particularly in the first few days. Doctor, as you know, patients on warfarin or similar agents are at an increased risk for GI bleeding when administered concomitantly with an NSAID.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

If further probed, refer to the PI:
In single and multiple-dose studies in healthy individuals receiving both warfarin and rofecoxib, prothrombin time (measured as INR) was increased by approximately 8% to 11%. In post-marketing experience, bleeding events have been reported, predominantly in the elderly, in association with increases in prothrombin time in patients receiving VIOXX concurrently with warfarin. Standard monitoring of INR values should be conducted when therapy with VIOXX is initiated or changed, particularly in the first few days, in patients receiving warfarin or similar agents.

Submit a PIR if appropriate.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:
VIOXX PI ⇒ Precautions ⇒ Drug Interactions ⇒ Warfarin (V51)

*INR – International Normalized Ratios. This is a standardized way of measuring the degree of anti-coagulation produced by warfarin.

Sr. I receive this letter from Searle about Celebrex and warfarin. What can you tell me about that and VIOXX?

Doctor, for information about celecoxib and warfarin, you should talk to your Searle or Pfizer representative.

However, I can tell you about the concomitant use of VIOXX and warfarin. In single and multiple-dose studies in healthy individuals receiving both warfarin and rofecoxib, prothrombin time (measured as INR) was increased by approximately 8% to 11%. In post-marketing experience, bleeding events have been reported, predominantly in the elderly, in association with increases in prothrombin time in patients receiving VIOXX concurrently with warfarin. Standard monitoring of INR values should be conducted when therapy with VIOXX is initiated or changed, particularly in the first few days, in patients receiving warfarin or similar agents.

Finally, doctor, as you know, patients on warfarin or similar agents are at an increased risk for GI bleeding when administered concomitantly with an NSAID.

Submit a PIR if appropriate.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:
VIOXX PI ⇒ Precautions ⇒ Drug Interactions ⇒ Warfarin (V51)
VIOXX PI ⇒ Warnings ⇒ GI Effects, 4th paragraph

*INR – International Normalized Ratios. This is a standardized way of measuring the degree of anti-coagulation produced by warfarin.

I'm concerned about the potential edema that occurs with VIOXX

COPY

Clarify:
What are your specific concerns regarding edema?

If the physician's concern is the overall incidence of edema with once daily VIOXX, then respond:
Doctor, edema is reported with all NSAIDs and is thought to result from cyclooxygenase inhibition in the kidney. Clinical trials with once daily VIOXX 12.5 and 25 mg have shown renal effects such as edema similar to those observed with comparator NSAIDs. In these studies, the incidence rates for lower extremity edema were as follows: (In the AE table, point to row on edema under Body As A Whole)

VIOXX 12.5 mg or 25 mg once daily - 3.7%
Ibuprofen 2400 mg – 3.8%
Diclofenac 150 mg –3.4%
Placebo – 1.1%

Also, it is important to note that in these same studies the discontinuation rate due to lower extremity edema was low-0.2%.

NOTE: Use the Renal Card to support this discussion.

If physician is concerned about a dose related increase of edema with once daily VIOXX 50 mg, then respond:

Doctor, edema is reported with all NSAIDs and is thought to result from cyclooxygenase inhibition in the kidney.

Regarding the safety of once daily VIOXX 50 mg, let me explain where the use of 50 mg is recommended. 50 mg is recommended for use in acute pain in adults and is not recommended for OA. In the analgesia studies, the renal effects of once daily VIOXX – such as edema-were generally similar to comparator NSAIDs.

The 50 mg dose, while not recommended for OA, has been studied in clinical trials for up to 6 months to evaluate the GI safety of VIOXX. In these trials, the incidence of lower extremity edema was 6.3% for 50 mg. In the 6-week to 6-month studies with 12.5 or 25 mg, the incidence of lower extremity edema was 3.7% and the discontinuation rate was low-0.2%. Are you concerned about a 3.7% incidence rate of lower extremity edema in your OA patients?

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:
VIOXX PI ⇒ Adverse Reactions ⇒ OA ⇒ Table and second paragraph (V59)
VIOXX PI ⇒ Precautions ⇒ Fluid Retention and Edema (V35)

COPY

[redacted]

Clarify: Doctor, what is your true concern?

If physician mentions denial of an RA indication, respond:
Doctor, Merck was not denied any indications. Once daily VIOXX is indicated for relief of the signs and symptoms of OA; management of acute pain in adults, and for the treatment of primary dysmenorrhea. These represent all of the indications that Merck submitted to the FDA for the approval of once daily VIOXX.

(Note: If the physician ask specific question regarding the VIOXX GI Outcomes trial, you may provide the PIR with the recent bulletin, in accordance with the instructions in that bulletin, and submit additional PIRs as requested.)

If appropriate, state: Last month when I was in, you stated that the majority of your arthritis patients suffer from OA. I would like for us to discuss how once daily VIOXX could benefit these patients.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

(After close: If you need information on the use of VIOXX in RA, I can submit a PIR.)

If the physician is concerned about the anti-inflammatory effect, see obstacle #6.

Reference:
VIOXX PI ⇒ Indications and Usage (V22)
VIOXX PI ⇒ Clinical Pharmacology ⇒ Mechanism of Action (V3)

[redacted]

Doctor, the Mechanism of Action section of the package insert for once daily VIOXX clearly states: "VIOXX is a nonsteroidal anti-inflammatory drug that exhibits anti-inflammatory, analgesic, and anti-pyretic activities in animal models." Once daily VIOXX 12.5 and 25 mg reduced the signs and symptoms of OA as effectively as 2400 mg of ibuprofen. Also, once daily VIOXX produced significant reductions in joint stiffness upon first awakening in the morning. Doctor, as you know, morning stiffness is one indicator of inflammation.

In addition, let me point out that in the label it also states "because of the anti-inflammatory effects of VIOXX, the pharmacological activity of VIOXX in reducing inflammation, and possibly fever, may diminish the utility of these diagnostic signs in detecting infectious complications of presumed noninfectious, painful conditions."

Doctor, would you agree that once daily VIOXX has anti-inflammatory effects?

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:
VIOXX PI ⇒ Clinical Pharmacology ⇒ Mechanism of Action (V3)
VIOXX PI ⇒ Clinical Studies ⇒ OA (V16)
VIOXX PI ⇒ Precautions ⇒ General (V31)

7. Can VIOXX be used in patients using low-dose aspirin?

There is no contraindication for concomitant use with low-dose aspirin.

Let me share with you the experience we have on the concomitant use of once daily VIOXX and low-dose aspirin. At steady state, once daily VIOXX 50 mg had no effect on the anti-platelet activity of low-dose (81 mg once daily) aspirin.

I should also remind you that once daily VIOXX is not a substitute for aspirin for cardiovascular prophylaxis and that concomitant administration of low-dose aspirin with once daily VIOXX may result in an increased risk of GI ulceration or other complications compared with use of once daily VIOXX alone.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:
VIOXX PI ⇒ Precautions ⇒ Drug Interactions ⇒ Aspirin (V41)

[redacted]

No. Doctor, let me show you the contraindications section of the label. Once daily VIOXX is not contraindicated for patients with known sulfonamide allergies, commonly known as "sulfa allergies."

Unlike once daily VIOXX, celecoxib is contraindicated in patients with sulfonamide allergies. Celecoxib contains a sulfonamide group (S-NH_2), which is associated with sulfa allergies. This contraindication is based on the specific chemical structure of celecoxib and is not a class effect. Sulfonamide allergies are common drug allergies in the US population and allergic reactions can range from mild to more serious.

Once daily VIOXX offers simplicity, with no sulfonamide allergy contraindication.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:
VIOXX PI ⇒ Contraindications (V23)

COPY

3. Why wasn't VIOXX 50 mg studied for longer than five days in acute pain?

To obtain an indication for the management of acute pain in adults, all analgesic drugs are studied in short-term standard pain models as defined by the FDA. The maximum time for these studies for once daily VIOXX was 5 days. However, let me point out that while it is not a recommended dose for OA, once daily VIOXX 50 mg was studied out to 6 months to evaluate GI safety. In these studies, the general safety profile of once daily VIOXX 50 mg was similar to the recommended doses, except for a higher incidence of GI symptoms, lower extremity edema, and hypertension. Also, let me point out that once daily VIOXX is indicated for the treatment of acute pain. The studies that support this acute pain indication lasted up to 5 days. But as I mentioned, while it is not a recommended OA dose, once daily VIOXX 50 mg was studied for up to 6 months in OA patients – so the profile is well defined in the circular.

If further probed: **"But, I'm worried about GI safety long-term."** Doctor, in two identical studies of OA patients receiving once daily VIOXX 25 or 50 mg for up to 24 weeks, once daily VIOXX demonstrated significantly fewer endoscopic ulcers than ibuprofen.

Once daily VIOXX also has GI event data from clinical trials up to one year. Among 3,357 patients who were treated with once daily VIOXX 12.5, 25, and 50 mg in controlled clinical trials of 6-weeks to 1 year, a total number of four patients experienced a serious upper GI event. Two patients experienced an upper GI bleed within 3 months (0.06%); one experienced an obstruction within 6 months; and one experienced an upper GI bleed within 12 months, for a total incidence of 0.12% over 1 year.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:
VIOXX PI ⇒ Clinical Studies ⇒ Analgesic Studies (V17)
VIOXX PI ⇒ Clinical Studies ⇒ OA (V16)

COP

[redacted]

Doctor, that is not what the circular states. The circular states that the recommended initial dose of VIOXX for the management of acute pain and the treatment of primary dysmenorrhea is 50 mg once daily. Subsequent doses should be 50 mg once daily as needed. The use of VIOXX for more than 5 days in the management of pain has not been studied.

Let me explain why these studies were designed this way. To obtain an indication for the management of acute pain in adults, all analgesic drugs are studied in short-term standard pain models as defined by the FDA. The maximum duration of these studies for once daily VIOXX was 5 days.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

If challenged further by the physician:
~~However, let me also point out that while 50 mg is not a~~ recommended dose for OA, once daily VIOXX 50 mg was studied out to 6 months in OA patients. In these studies, the general safety profile of once daily VIOXX 50 mg was similar to the recommended doses for OA, except for a higher incidence of GI symptoms, lower extremity edema and hypertension.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:
VIOXX PI ⇒ Indications and Usage (V22)
VIOXX PI ⇒ Dosage and Administration ⇒ Osteoarthritis (V65) and Management of Acute Pain and Treatment of Primary Dysmenorrhea (V66)

COPY

Q: Why didn't you compare VIOXX to higher doses of ibuprofen or naproxen sodium for the management of pain?

To obtain an indication for the management of acute pain in adults, a drug must be studied in standard pain models as defined by the FDA. As it states in the ibuprofen PI, in clinical studies using doses of ibuprofen greater than 400mg are no more effective than the 400mg dose in analgesia. Also, the maximum recommended dose of naproxen for analgesia is 550 mg.

In acute analgesic models of post-orthopedic surgical pain, post-operative dental pain and primary dysmenorrhea, once daily VIOXX relieved pain that was rated by patients as moderate to severe. In post-surgical dental pain studies, the onset of action with a single 50mg dose of once daily VIOXX occurred within 45 minutes.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:
VIOXX PI ⇒ Clinical Studies ⇒ Analgesia (V17)

[redacted]

Whether you're treating OA or acute pain, once daily VIOXX is always a simple, one tablet, once daily dose.

12.5 mg or 25 mg once daily for OA

Once daily VIOXX 12.5mg is the starting dose for OA. If a patient requires greater pain relief, you have the flexibility to increase the dose to 25mg once daily at no additional cost to the patient.

50 mg once daily for Acute Pain and Primary Dysmenorrhea

In patients with moderate to severe acute pain, the dose is 50mg once daily. Once daily VIOXX relieved moderate to severe pain following orthopedic surgery, dental surgery and primary dysmenorrhea.

In addition to the simplicity of once daily dosing, once daily VIOXX also adds the flexibility of oral suspension for both strengths.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

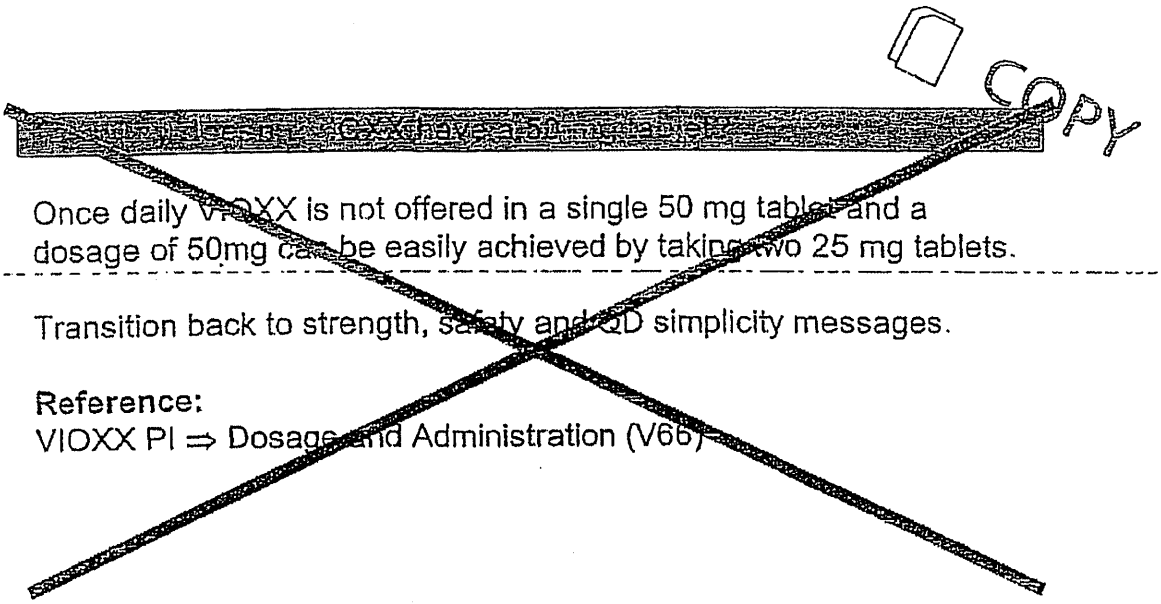
Reference:
VIOXX PI ⇒ Dosage and Administration (V65-V67)

[redacted] COPY

No dosage adjustment is recommended for patients with mild to moderate renal impairment. Use of once daily VIOXX in patients with advanced renal disease is not recommended because no safety information is available regarding the use of once daily VIOXX in these patients.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

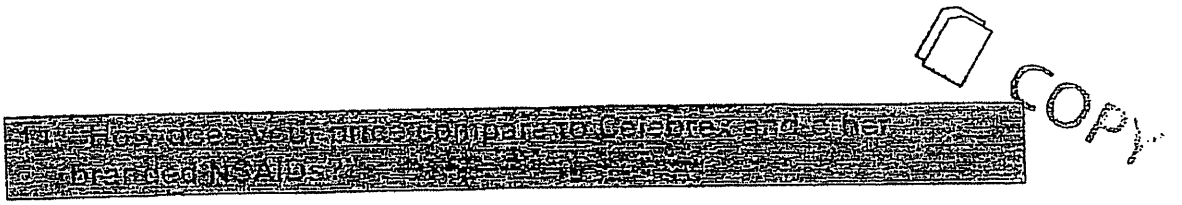
Reference:
VIOXX PI ⇒ Precautions ⇒ Renal Effects (V33)
VIOXX PI ⇒ Precautions ⇒ Fluid Retention and Edema (V35)



Once daily VIOXX is not offered in a single 50 mg tablet and a dosage of 50mg can be easily achieved by taking two 25 mg tablets.

Transition back to strength, safety and QD simplicity messages.

Reference:
VIOXX PI ⇒ Dosage and Administration (V66)



11. How does your price compare to Celebrex and other branded NSAIDs?

Doctor, the catalog price for once daily VIOXX is $2.02 for both 12.5 mg and 25 mg, offering your patients one of the best values available.

The catalog price for celecoxib is $2.38 for 100mg bid and $2.02 for 200 mg qd.

The catalog price for VIOXX 12.5 and 25mg is less expensive than the catalog prices for the usual daily doses of Arthrotec, Relafen, Daypro, and Voltaren.

In addition, the catalog price for the oral suspension of once daily VIOXX is competitive with other NSAIDs at $3.00.

This price comparison does not establish that products have comparable efficacy. These prices reflect direct cost and do not reflect actual costs paid by consumers.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

(For your reference, the average wholesale price (AWP) for once daily VIOXX is $2.42 for both 12.5 mg and 25 mg. AWP for celecoxib is $2.86 for 100 mg BID and $2.42 for 200 mg qd.
AWP for the oral suspension of once daily VIOXX is competitive with other NSAIDs at $3.60.)

[redacted] COPY

The 17 hour half-life of once daily VIOXX is entirely consistent with its once daily dosing. In all OA studies, lasting from 6 to 86 weeks with 3900 patients, once daily treatment with VIOXX 12.5 and 25 mg in the morning was associated with a significant reduction in joint stiffness upon first awakening in the morning. At doses of 12.5 and 25 mg once daily, the effectiveness of once daily VIOXX was shown to be comparable to ibuprofen 800mg TID and diclofenac 50 mg TID.

If probed further on half life:
Doctor, many drugs with half-lives shorter than 24 hour are effective when dosed once a day, for example Singulair, Prinivil, and Zocor.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:
VIOXX PI ⇒ Clinical Pharmacology ⇒ Excretion (V8)
VIOXX PI ⇒ Clinical Studies ⇒ OA (V16)
SINGULAIR® PI ⇒ Clinical Pharmacology ⇒ Excretion
PRINIVIL® PI ⇒ Clinical Pharmacology ⇒ Excretion
ZOCOR® PI ⇒ Clinical Pharmacology ⇒ Excretion

[redacted] Copy

or

[redacted]

Doctor, you are correct when you say that COZAAR is metabolized by cytochrome P450 enzymes. COZAAR has been evaluated for safety in more than 3300 patients treated for hypertension. The overall incidence of adverse experiences reported with COZAAR in clinical studies was similar to placebo. No significant drug-drug pharmacokinetic interactions have been found in interaction studies with hydrochlorothiazide, digoxin, warfarin, cimetidine, and phenobarbital. COZAAR has been extensively used in clinical practice and clinical study settings for over four years with millions of patients treated. Clinical experience with COZAAR is well documented.

In vitro studies indicate that cytochrome P450 2C9 and 3A4 are involved in the biotransformation of losartan to its active metabolite. Conversion of losartan to its active metabolite after intravenous administration is not affected by ketoconazole, an inhibitor of P450 3A4. The pharmacodynamic consequences of concomitant use of losartan and inhibitors of P450 2C9 have not been examined.

Celecoxib is metabolized by P450 2C9 and is an inhibitor of P450 2D6. The package circular states that the co-administration of celecoxib with drugs that are known to inhibit 2C9 should be done with caution. It also states that there is a potential for an in vivo drug interaction with drugs that are metabolized by P450 2D6.

Doctor, let me also note that VIOXX is not primarily metabolized by cytochrome P450 enzymes and is not known to inhibit enzymes of P450.

If you have additional questions regarding the P450 system and/or the implications for the products we discussed, I would be happy to submit a Professional Information Request to our Medical Services Department.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:

VIOXX PI ⇒ Clinical Pharmacology ⇒ Metabolism (V7)
COZAAR® PI ⇒ Clinical Pharmacology ⇒ General
COZAAR® PI ⇒ Adverse Reactions
COZAAR® PI ⇒ Precautions ⇒ Drug Interactions
Celecoxib PI ⇒ Precautions ⇒ Drug Interactions ⇒ General (C36)

[redacted]

or

[redacted]

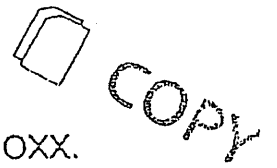
Doctor, you are correct when you say that ZOCOR is metabolized via CYP450. ZOCOR has been extensively used in clinical practice and clinical study settings for over 10 years with millions of patients treated and tens of thousands of patients studied in controlled trials. Clinical experience with ZOCOR is well documented.

For ZOCOR, we know that the risk of myopathy appears to be increased by high levels of HMG-CoA reductase inhibitory activity in plasma. Certain drugs that inhibit this pathway can raise the plasma levels of simvastatin and may increase the risk of myopathy. Therefore, physicians contemplating concomitant therapy with ZOCOR and a drug that inhibits the P450 3A4 pathway should carefully weigh the potential benefits and risks of combined therapy and monitor for signs and symptoms of myopathy.

Celecoxib, on the other hand, is metabolized by P450 2C9 and is an inhibitor of P450 2D6. The package circular states that the co-administration of celecoxib with drugs that are known to inhibit 2C9 should be done with caution. It also states that there is a potential for an in vivo drug interaction with drugs that are metabolized by P450 2D6.

Doctor, let me also note that VIOXX is not primarily metabolized by the P450 system and is not known to inhibit the P450 system.

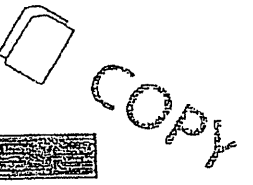
If you have additional questions regarding the P450 system and/or the implications for the products we discussed, I would be happy to submit a Professional Information Request to our Medical Services Department.



Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:

VIOXX PI ⇒ Clinical Pharmacology ⇒ Metabolism (V7)
ZOCOR® PI ⇒ Warnings ⇒ Myopathy caused by drug interactions
Celecoxib PI ⇒ Clinical Pharmacology ⇒ Metabolism (C8)



3. The pain studies for VIOXX were not well designed.

Clarify: Which pain study are you referring to and why do you feel it was not well designed?

- **If the physician is concerned about the head-to-head study comparing VIOXX to Celebrex, offer to submit a PIR.**

- **If the physician is concerned because VIOXX was compared to 400 mg Ibuprofen, use the response offered in obstacle #10 in the Obstacle Response Guide and respond:**

To obtain an indication for the management of acute pain in adults, a drug must be studied in standard pain models as defined by the FDA. As it states in the ibuprofen PI, in clinical studies using doses of ibuprofen greater than 400mg are no more effective than the 400 mg dose in analgesia. Also, the maximum recommended dose of naproxen for analgesia is 550 mg.

In acute analgesic models of post-orthopedic surgical pain, post-operative dental pain and primary dysmenorrhea, once daily VIOXX relieved pain that was rated by patients as moderate to severe. In post-surgical dental pain studies, the onset of action with a single 50mg dose of once daily VIOXX occurred within 45 minutes.

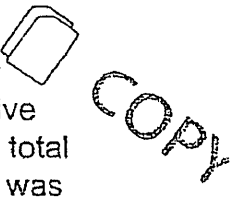
Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:
VIOXX PI ⇒ Clinical Studies ⇒ Analgesia (V17)

- **If the physician is concerned about the different dosing regimens, respond:**

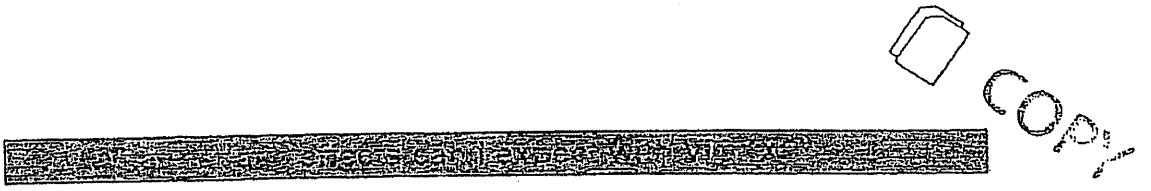
Doctor, this is a single dose model. It is a standard model designed to assess the analgesic effect of an agent. It was not designed to compare the dosing regimens of the agents, in this

instance, once daily VIOXX versus 3 times a day Ibuprofen or twice daily naproxen. However, it does demonstrate the relative efficacy of the two agents on onset of action, peak effect, and total pain relief over 8 hours. On the measures, once daily VIOXX was generally similar to the comparator NSAIDs.



Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:
VIOXX PI ⇒ Clinical Studies ⇒ Analgesia (V17)



Clarify: What specific hepatic effects are you concerned about?

If physician is concerned about liver function testing (LFTs), respond:
In controlled clinical trials of VIOXX, the incidence of borderline elevations of liver tests at doses of 12.5 and 25 mg daily was comparable to the incidence observed with ibuprofen and lower than that observed with diclofenac. In placebo-controlled trials, approximately 0.5% of patients taking once daily VIOXX 12.5 or 25 mg and 0.1% of patients taking placebo had notable elevations of ALT or AST. A patient who has an abnormal liver test while on once daily VIOXX should be monitored carefully for evidence of a more severe hepatic reaction.

Use of VIOXX is not recommended in patients with moderate or severe hepatic insufficiency.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

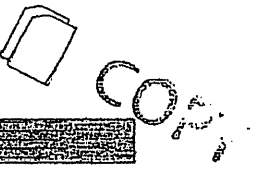
Reference:
VIOXX PI ⇒ Precautions ⇒ Hepatic Effects (V32)

If physician is concerned about metabolism, respond:
Doctor, metabolism of once daily VIOXX is primarily mediated through reduction by cystolic enzymes in the liver. It is not primarily metabolized by the P450 system and is not known to inhibit the P450 system in the liver.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:
VIOXX PI ⇒ Clinical Pharmacology ⇒ Metabolism (V7)

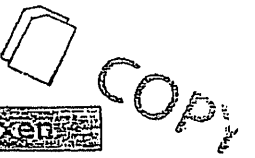
[redacted] with ACE Inhibitors



Doctor, as stated in the prescribing information, once daily VIOXX can be used concomitantly with ACE inhibitors. All NSAIDs may diminish the antihypertensive effect of ACE inhibitors. The prescribing information for once daily VIOXX states "In patients with mild to moderate hypertension, administration of 25 mg daily of VIOXX with the ACE inhibitor benazepril, 10 to 40 mg for 4 weeks, was associated with an average increase in mean arterial pressure of about 3 mm Hg compared to ACE inhibitor alone." Remember, all NSAIDs may diminish the antihypertensive effect of ACE inhibitors. Therefore, this effect is not unique to VIOXX.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:
VIOXX PI ⇒ Precautions ⇒ Drug Interactions ⇒ ACE inhibitors (V40)



2. VIOXX is not comparable to a single dose of Naproxen

Clarify:
Doctor, why do you say that?

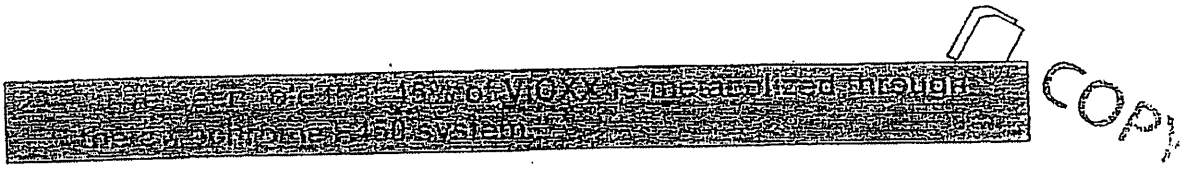
If the physician replies "It states in your product circular that VIOXX 50mg once daily was comparable to naproxen 550mg. This would seem to indicate that you are not comparable to 550mg bid," then respond:

Doctor, that statement is derived from single dose studies and is not intended to compare or draw conclusions about the efficacy of VIOXX or Anaprox over a 24 hour period. It was not designed to compare the dosing regimens of the agents. The single dose analgesia study was designed to compare time of onset, peak effect and total pain relief over 8 hours. In OA studies, once daily VIOXX 12.5mg and 25mg were comparable to ibuprofen 800mg tid and diclofenac 50mg tid. In each study, both 12.5mg and 25mg of VIOXX once daily were comparable to the comparator NSAIDs. Would you agree that 800 mg of ibuprofen tid and 50 mg of diclofenac tid were good NSAID comparators to demonstrate the efficacy of once daily VIOXX in OA over a full 24 hours? Will you try once daily VIOXX in your acute pain and OA patients?

If the physician replies "You only compared yourself to 550mg of naproxen in your pain studies" refer to the obstacle "The pain studies for VIOXX were not well designed" in the Obstacle Response Guide, #18.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

For Representatives background, naproxen sodium is Anaprox, and naproxen is Naprosyn.



I would like to clarify that in general, once daily VIOXX is metabolized primarily through reduction by cytosolic enzymes in the liver, not primarily through the P450 system. Cytochrome P450 plays a minor role in the metabolism of once daily VIOXX.
The inhibition of P450 3A4 activity by administration of ketoconazole 400 mg daily did not affect the disposition of VIOXX. However, induction of general hepatic activity by administration of the non-specific inducer rifampin 600 mg daily produced a 50% decrease in VIOXX plasma concentrations.

If you are interested in further information on the metabolism of once daily VIOXX, I'd be happy to submit a PIR.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:
VIOXX PI ⇒ Clinical Pharmacology ⇒ Metabolism (V7)

Background Information
Cytochrome P450: Inhibition and Induction (referenced from the Analgesic and Anti-Inflammatory Training Program, Module 5, pages 31-32).

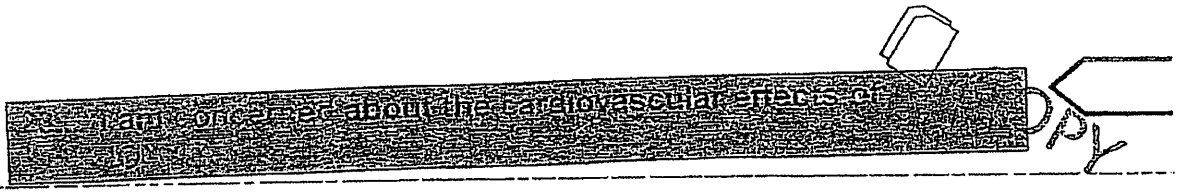
Inhibition
Inhibition of specific CYP450 enzymes can also affect the conversion of a drug to its active metabolite. Significant drug interactions may occur when NSAIDs that are metabolized through the CYP450 system are administered together with drugs that inhibit enzymes of the CYP450 systems. Concomitant administration of a drug with a known inhibitor of cytochrome P450 enzymes can alter the relative amounts of parent and metabolite that end up in the general circulation. For example, concomitant administration of fluconazole, a known inhibitor of CYP2C9, and celecoxib results in an increase in

celecoxib plasma concentrations due to the inhibition of celecoxib metabolism via CYP2C9 by fluconazole.

In vitro studies indicate that celecoxib, although not a substrate, is an inhibitor of CYP2D6. Therefore, there is a potential for an in vivo drug interaction with drugs that are metabolized by CYP2D6. Some examples of drugs that are metabolized by CYP2D6 are certain antidepressants (e.g., tricyclic antidepressants (TCAs) and selective serotonin re-uptake inhibitors (SSRIs), antipsychotics (e.g., haloperidol), and narcotics (e.g., codeine). Coadministration of these agents with celecoxib may result in increased serum concentrations of these drugs.

Induction

Drug-drug interactions can also occur when one drug induces the metabolism of another by increasing the synthesis or reducing the degradation of CYP450 enzymes, as shown in Figure 13. In this case, the clearance of the drug will be increased and the pharmacological effects decreased. Increased synthesis of CYP450 protein (which leads to an increase in CYP450) activity) can be associated with exposure to certain drugs or environmental agents. Enzyme induction can lead to an increased rate of drug metabolism and corresponding decreases in the availability of the parent drug. For example, indinavir is metabolized by CYP3A4. Therefore, the drug rifampin, a potent inducer of CYP3A4, should not be co-administered because it may lead to markedly diminished plasma concentrations of indinavir.



Clarify:
What is your specific concern?

The physician may respond:
(A) "I am hesitant to use VIOXX in my patients because it may worsen CHF," or
(B) "VIOXX has the potential to increase the risk of MI."

Response to (A) "I am hesitant to use VIOXX in my patients because it may worsen CHF."
Doctor, as you know, there are precautions you should take when prescribing any NSAID for your patients with CHF. Because once daily VIOXX® is an NSAID, you should consider taking these same precautions when considering the use of once daily VIOXX® for this specific patient population.

Clinical trials with once daily VIOXX® 12.5 mg and 25 mg have shown renal effects such as hypertension and lower extremity edema similar to those observed with comparator NSAIDs. VIOXX® should be used with caution and should be introduced at the lowest recommended dose in patients with fluid retention, hypertension, or edema.

(NOTE: If the physician asks about concomitant use with ACEIs, refer to Obstacle Response No. 20.)

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:
VIOXX PI ⇒ Precautions ⇒ Renal Effects (V33)
VIOXX PI ⇒ Precautions ⇒ Fluid Retention and Edema (V35)

Response to (B) "VIOXX increases the risk of MI."

Doctor, once daily VIOXX has no effect on platelet aggregation, and therefore would not be expected to demonstrate reductions in MI or other CV events. Agents such as low-dose aspirin are routinely prescribed for CV patients for their effect on the inhibition of platelet aggregation. Therefore, once daily VIOXX® is not a substitute for aspirin for cardiovascular prophylaxis. However, once daily VIOXX 50 mg had no effect on the anti-platelet activity of low dose (81 mg daily) aspirin when the two were given together.

(Refer to Obstacle Response No. 7.)

If probed further:
Offer to submit a PIR.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:
VIOXX PI ⇒ Precautions ⇒ Aspirin (V41)

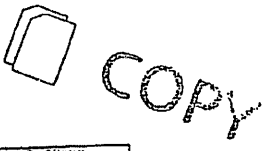
[redacted]

Doctor, it is important to note that the time period you refer to, 1 to 2 weeks, was the predetermined initial time intervals in the study at which pain relief was measured. Patient's pain relief was simply not assessed earlier than that by design. The objective of these trials (up to one year) was to evaluate study endpoints over the course of the trial-not onset of action. These were not studies of onset of action

If you would like specific information on the onset of action of once daily VIOXX in acute pain, let's look at the comparison to naproxen sodium (Anaprox) in dental pain which showed an onset of action of VIOXX 50 mg within 45 minutes.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:
VIOXX PI⇒Clinical Studies PI⇒OA (V16)
VIOXX PI⇒Clinical Pharmacology ⇒ Pharmacokinetics ⇒ Absorption (V4)
VIOXX PI⇒Clinical Studies□Analgesia, including Dysmenorrhea (V17)
Celecoxib PI⇒ Clinical Pharmacology ⇒ Pharmacokinetics ⇒ Absorption (C4)



~~Is your concern with VIOXX pre- or post-operatively?~~

Clarify: Dr. what specifically is your concern?

If the concern is with bleeding time (pre and post-operatively), respond:
Once daily VIOXX® has not been studied in a pre-operative setting. I cannot make a recommendation regarding pre-operative use.

In studies of healthy volunteers who had not undergone surgery, at multiple doses of up to 375 mg daily up to 12 days, VIOXX® had no effect on bleed time relative to placebo. Similarly, bleeding time was not altered in a single dose study with 500 or 1000mg of VIOXX®.

Additionally, VIOXX® 50 mg has shown no effect on platelet aggregation. ~~Also, once daily VIOXX 50 mg had no effect on the anti-~~ platelet activity of low dose (81 mg daily) aspirin when the two were given together.

If requesting further information, please submit a request.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

If the concern is the management of acute pain, post-operatively, respond:
In order to obtain an acute pain indication, VIOXX® was demonstrated to provide effective pain relief in 3 acute pain models.

Two of the pain models involved surgery – the post-orthopedic surgical model and the post-operative dental pain model. The post-orthopedic surgery studies involved patients with knee or hip replacement. Patients received their first dose of VIOXX®, on average, 46 hours after surgical procedure (range 17 to 97 hours). In our acute dental pain study, VIOXX® provided onset of pain relief within 45 minutes.

Dr., in contrast, Celebrex is not indicated for the management of acute pain.

COPY

If further information is requested, offer to submit a PIR.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Reference:
VIOXX PI ⇒ Clinical Studies ⇒ Platelets (V21)

26. "I'm concerned about the safety profile of [redacted]"

Clarify:
Doctor, specifically what safety concerns are you referring to?

If the physicians' concern is renal safety or edema:
Refer to obstacle # 12, 4

If the physicians' concern relates to hepatic effects or cardiovascular safety:
Refer to obstacle # 19,23

If the physicians' concern is whether the rate of ulcers increases over time when treating patients with VIOXX, respond with the following:

Doctor, in order to address your concerns, I would like to discuss the extensive GI endoscopy program that has been conducted for VIOXX®. In two identical, large trials, the **cumulative** incidence of ulcers with patients taking VIOXX 25 mg and 50 mg once daily (2 to 4X the dose used for osteoarthritis) was studied. The results with VIOXX showed significantly fewer endoscopic ulcers than with ibuprofen 2400 mg at weeks12 and 24. (Refer to VIOXX® PI, Clinical Trials.)

Doctor, I would like to bring to your attention a few important factors regarding our endoscopy study design:

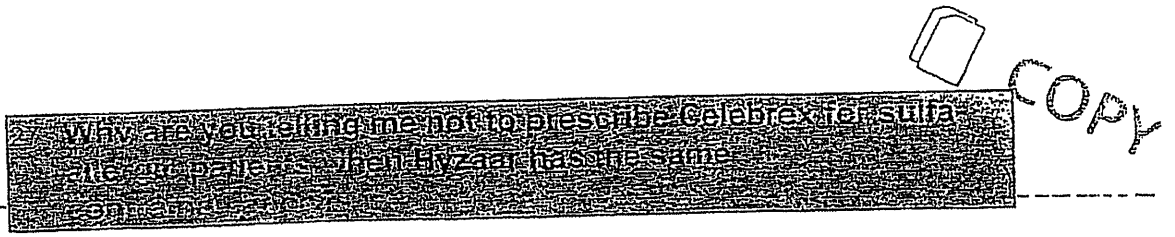
First, "cumulative rates" include all patients who develop an ulcer up to a specified point in time. In other words, the rates shown at week 24 include all endoscopic ulcers detected by week 12 and all endoscopic ulcers detected between weeks 12 and 24. This method assures that patients developing ulcers at any time during the study are represented in the overall risk assessment.
As noted in the attached Laine reprint (page 780, second full paragraph), when referencing the endoscopy trials for VIOXX®,

"Ulcer rates in the first 3 months of the study were not significantly different compared to the second three months in the rofecoxib groups or in the ibuprofen groups (4.1% vs. 5.5% in the 25 mg rofecoxib group, 7.3% vs. 7.4% in the rofecoxib 50 mg group, and 27.7% vs. 18.2% in the ibuprofen group)". Please refer to the Important Considerations for Endoscopy Studies as noted in the detail aid.

Please provide appropriate and referenced balancing throughout product discussions with healthcare professionals.

Note: We have heard reports from the field that Searle/Pfizer representatives are describing the results as "additive rates". Additive rates evaluate an increase over a specified period of time and make assumptions that rates continue to increase by the same rate into the future.

The rates reported in this study are not additive rates.



Why are you telling me not to prescribe Celebrex for sulfa-allergic patients when Hyzaar has the same contraindication?

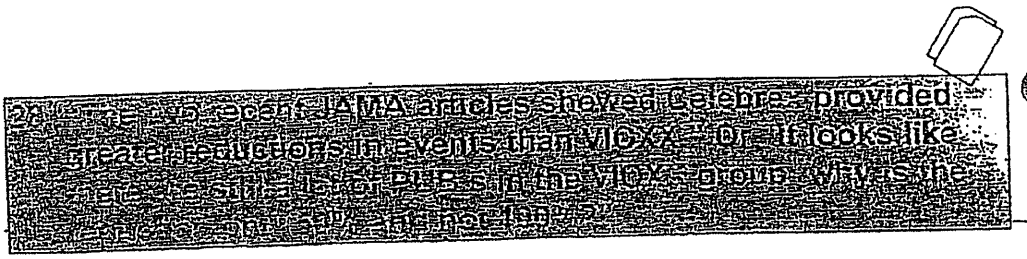
Dr., I can appreciate your concern. Let me clarify Merck's view of this and every other contraindication for our product.

The fact remains that a contraindication is just that – a contraindication. At no time will Merck ever suggest that you prescribe an agent to a patient who is contraindicated for its use.

As you know, use of hydrochlorothiazide in patients who are allergic to sulfonamides is contraindicated. Hyzaar, which is losartan plus hydrochlorothiazide, is contraindicated for use in patients with hypersensitivity to other sulfonamide-derived drugs. However, losartan, (Cozaar) alone is not contraindicated in these patients. We do not, have not, and never will recommend the use of Hyzaar for patients who have sulfonamide allergies. Cozaar is not contraindicated for patients who have a sulfonamide allergy and can be prescribed for these patients who need control of their BP.

Regarding the Coxib class, **VIOXX does not have a contraindication for sulfonamide allergic patients** – Celebrex does.

(Note: If you have not already discussed Cozaar/Hyzaar with this physician on this call, take the opportunity to initiate a discussion regarding these products after you close your product discussion for VIOXX. One suggested transition may be, "Just as we have discussed appropriate patients to prescribe VIOXX for, I'd like to discuss appropriate patients for therapy with Cozaar, Hyzaar 50/12.5 and Hyzaar 100/25...")



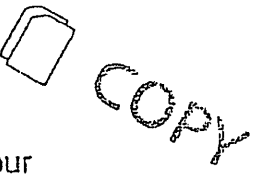
Note: Physician is referring to the JAMA article, November 24, 1999 issue, Volume 282, No. 20

Representative Response:

Actually those were different types of studies. **(See below or in the cover bulletin for background information)**

The JAMA article on VIOXX is a combined analysis of PUBs, Perforation, symptomatic Ulcers and Bleeds from all 8 double bind, randomized phase 2b/3 OA trials. The Celebrex article, which is the information currently contained in their PI, is a prospective endoscopy trial with Celebrex, comparator NSAIDs and placebo. This is similar to the study I have been discussing with you from our package circular, which compares VIOXX to Ibuprofen, and placebo. The JAMA study on VIOXX was designed to compare VIOXX to the comparator NSAIDS, not placebo. No one knows what the background rate of PUBs in patients treated with placebo would be, but we know it is not zero.
It would be inaccurate to compare the JAMA articles on VIOXX and Celebrex because the endpoints (ulcers detected on surveillance endoscopy versus clinically significant events) are entirely different. Until head to head comparative trials are designed and completed, no conclusions can be drawn regarding relative GI safety between these agents.

Additional studies will need to be conducted to further support these conclusions. As stated in the VIOXX package insert (under the 044 endoscopy data), "the correlation between findings of endoscopic studies, and the relative incidence of clinically serious upper GI events that may be observed with different products, has not been fully established."



However, I can share with you information for VIOXX from our endoscopy trials. These results are listed in our package circular, in our detail aids and most recently were published in Gastroenterology. The lead author of the study was Dr. Loren Laine. Among 742 OA patients without ulcers on baseline endoscopy, the cumulative incidence of gastroduodenal ulcers ≥ 3mm with VIOXX (25 mg or 50 mg) was significantly ($p<0.001$) lower than ibuprofen.
Also, in controlled clinical trials summarized in our promotional literature, among 3357 patients who were treated with VIOXX 12.5 mg, 25 mg, and 50 mg, only (POB data):

- 2 of 3357 (0.06%) patients experienced a serious Clinical Upper GI event in the first 3 months
- and 4 of 3357 patients cumulative (0.12%) experienced a serious Clinical Upper GI event in the first 12 months.

Transition back to Laine reprint or detail aid to further discuss results with VIOXX and deliver Top 5 messages, provide appropriate balance and close the call.

Remember that you may not discuss or provide the JAMA article to your physicians. You must submit a PIR to address any additional concerns.

Background Information:

It is critical to understand the differences in the types of analyses that have been performed in the studies that are now being published in JAMA and Gastroenterology. Merck and Searle have both performed endoscopy studies comparing VIOXX® and celecoxib to NSAIDs. Both companies also have data from their combined clinical trials in their PIs describing what are termed "serious" upper GI events (Perforations, Obstructions and Bleeds, or POBs). These events are found during the course of clinical treatment, NOT during a scheduled endoscopy. In addition, Merck has just

published in JAMA the results of a PUB (Perforations, symptomatic Ulcers and Bleeds) analysis, data which is not in the PI for VIOXX®.

The first type of analysis is the endoscopy study. In this study patients are randomized to study drugs (or placebo) and undergo scheduled endoscopies (in the VIOXX® trials these were at baseline 6, 12, and 24 weeks). Ulcers that are seen through the endoscope are measured and counted. This provides a basis for comparing the effect of drugs on the gastric mucosa and is seen as a surrogate for clinically significant events, even if the ulcers seen are not symptomatic and do not actually lead to bleeding or other complications. This is the type of analysis done in the Laine paper published in Gastroenterology and the Searle paper in JAMA, data in the PIs for both VIOXX® and celecoxib.

It is sometimes considered more clinically relevant to compare drugs based on the number of clinical events that occur. Thus the second type of analysis is done, looking at events that occur during the trials. These occur at much lower rates than endoscopically visualized ulcers, so it requires many more patients to see any differences between drugs. Merck chose to measure PUBs (perforations, ulcers and bleeds) while the clinical event data in the PIs for VIOXX® and celecoxib measured POBs (perforations, obstructions and bleeds). The primary difference between these is the U – Ulcers that present due to clinical signs or symptoms. In the Merck JAMA paper, if any patient underwent endoscopy for cause (that is, the patient demonstrated symptoms that the physician judged worthy of follow-up) and ulcers were detected, these were included as events, along with the POBs. This explains why the rates of POBs in the PIs for celecoxib and VIOXX® are lower than the PUB rates shown in the JAMA paper on VIOXX®.

[redacted]

Doctor, it would have been great news for patients if Celebrex received an indication to prevent cancer, but what Celebrex actually received was an indication for a rare genetic disorder, familial adenomatous polyposis (FAP).

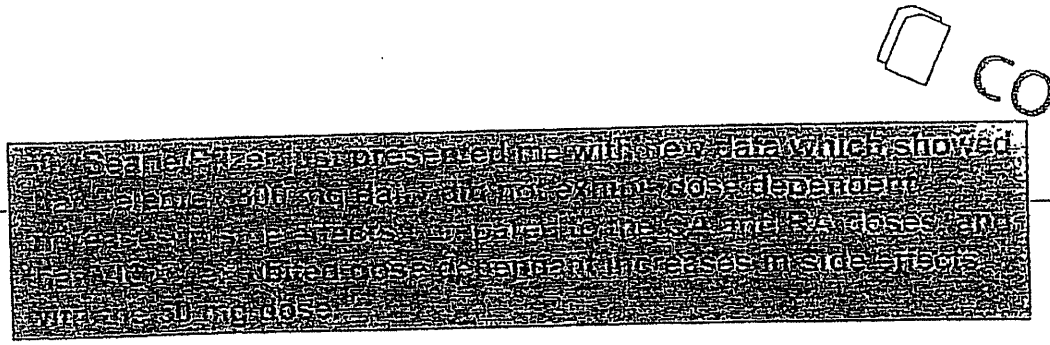
The indication is:

"to reduce the number of adenomatous polyps in familial adenomatous polyposis (FAP), as an adjunct to usual care". The indication further states, "It is not know whether there is a clinical benefit from a reduction in the number of colorectal polyps in FAP patients." The label also states that "treatment with Celebrex in FAP has not been shown to reduce the risk gastrointestinal cancer or the need for prophylactic colectomy or other FAP –related surgeries."

If pressed about whether Merck is conducting studies state,

"Doctor, I am not permitted to discuss uses that not included in the labeling for VIOXX. If you would like, I can submit a request for information to our medical services department."

Transition back to the HI COXIB or HI NSAID messages for VIOXX using the following statement, "So you can see, doctor, this is a new indication for a very rare disorder. Let's discuss much more common disorder-OA."



Note: You may have to probe to uncover the real obstacle. It may be presented as one of the following:

- Celebrex is now proven to be safer than VIOXX.
- Celebrex is a safer agent.
- Are there safety issues with VIOXX?

CLARIFY FIRST:

"Doctor, what is your concern regarding VIOXX? Is there a particular area of concern you want to discuss?"

RESOLVE

Doctor, Searle/Pfizer may be using their new FAP data to suggest that Celebrex 400mg bid, the dose used in the FAP studies, had an adverse event profile "*similar to that reported for patients in arthritis controlled trials*". It is important to realize that the FAP study included 83 patients, who were generally younger and otherwise healthy. This is a population very different from the patient population of OA studies.

It is important to realize that VIOXX 50mg is the recommended dose for acute pain or analgesia, and not a recommended dose for OA. In fact, our product circular states,

"*Approximately one thousand patients were treated with VIOXX in analgesia studies. The adverse experience profile in the*

analgesia studies was generally similar to those reported in the osteoarthritis studies."

Doctor, what this means is that when the 50mg dose was used in analgesia studies, it had a similar adverse experience profile as that which was seen with VIOXX 12.5 and 25mg in osteoarthritis studies.

If the doctor refers to the increased incidence of edema or hypertension listed under the Adverse Experiences table:

Doctor, the data that you are referring to are from the use of VIOXX 50mg in two, 6-month, OA, endoscopy trials, which evaluated the GI safety of VIOXX. VIOXX 50mg is not a recommended dose for the treatment of OA, but was used in these studies to determine GI safety. VIOXX, at both 25 and 50mg doses, yielded significantly fewer endoscopic ulcers than ibuprofen. Let me reiterate that in analgesia studies with VIOXX 50mg, the incidence of hypertension and edema was similar to that reported in the OA studies with VIOXX12.5 and 25mg.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Remember to provide appropriate balancing information as part of all product discussions.

[redacted]

Clarify:

Doctor, what has led to your concern that VIOXX causes dose-related increases in hypertension?

Resolve:

Doctor, according to the product circular for VIOXX, the incidence of hypertension reported in OA studies, regardless of causality, was 3.5% with the 12.5 or 25mg dose. For patients who were treated with VIOXX 50mg in analgesia studies, the VIOXX product circular states,

> *"Approximately one thousand patients were treated with VIOXX in analgesia studies. The adverse experience profile in the analgesia studies was generally similar to those reported in the osteoarthritis studies."*

Doctor, what this means is that when the 50mg dose was used in analgesia studies, it had a similar adverse experience profile as that which was seen with VIOXX 12.5 and 25mg in OA studies. VIOXX 50mg is not a recommended dose for OA.

If the doctor refers to the increased incidence of hypertension listed under the Adverse Experiences table:

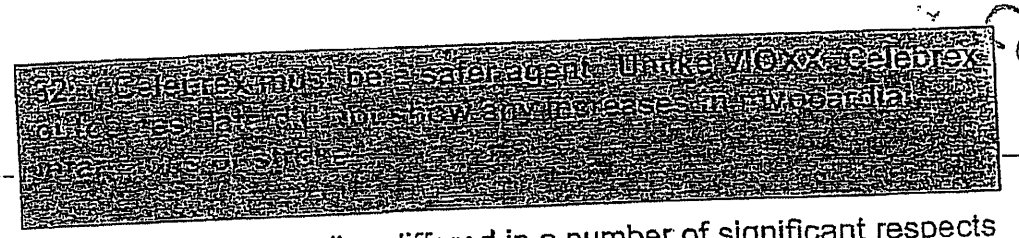
Doctor, the data that you are referring to is from the 6-month, OA, endoscopy trials, which were used to evaluate the GI safety of VIOXX. VIOXX 50mg is not a recommended dose for the treatment of OA, but was used in these studies to evaluate GI safety. VIOXX, at both 25 and 50mg doses yielded significantly fewer endoscopic

ulcers than ibuprofen. Let me reiterate that in analgesia studies with VIOXX 50mg, the incidence of hypertension was similar to that reported in the OA studies with VIOXX 12.5 and 25mg.

Doctor, have I addressed your concern with dose-related increases in hypertension with VIOXX?
Now let's talk about the benefits VIOXX offers you and your patients in the treatment of OA and acute pain.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Remember to provide appropriate balancing information as part of all product discussions.



The design of the studies differed in a number of significant respects and therefore the results of the two studies cannot be compared. So, let me tell you about the data for VIOXX from our OA clinical trials at the 12.5 mg and 25 mg doses.

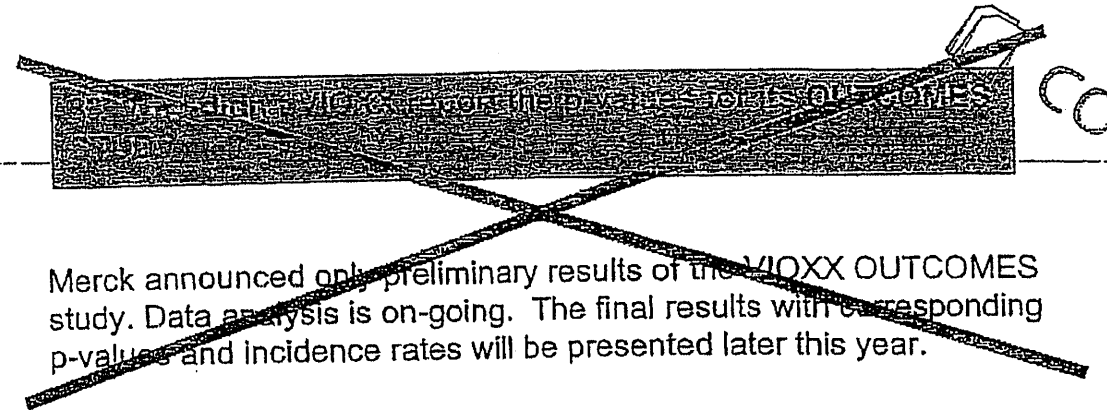
In an extensive review of all of our Phase III OA clinical trials, VIOXX did not show an increase in the incidence of thromboembolic events compared to placebo or the comparator NSAIDS.

You can feel confident that Merck has conducted OA clinical trials for VIOXX 12.5mg and 25mg daily in over 3600 patients with OA; approximately 1400 patients received VIOXX for 6 months or longer and approximately 800 patients for one year or longer. These trials included a placebo arm in the six week studies and two comparator NSAIDS, ibuprofen 2400 mg and diclofenac 150 mg daily. VIOXX 12.5mg and 25mg has shown to provide OA pain relief all day, all night and into the next morning.

Referring to the Adverse Events data, as listed in the package insert for VIOXX 12.5 mg and 25mg daily, the only Cardiovascular System adverse event experienced as occuring over 2% (in trials of six-weeks to six-months) was hypertension at **3.7 %** vs. comparators of ibuprofen 2400 mg daily at **3.0%** and diclofenac 150 mg daily at **1.6%.** In addition, stroke and MI each occurred in less than 0.1% of patients taking VIOXX in our OA clinical program.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Note: If the physician has questions regarding the hypertension & edema rates for VIOXX, please refer to obstacles #19 & #12. Also, the Renal Card (OAN #001962(1)) is an excellent resource that has been developed to directly address issues pertaining to hypertension & edema.



Merck announced only preliminary results of the VIOXX OUTCOMES study. Data analysis is on-going. The final results with corresponding p-values and incidence rates will be presented later this year.

[redacted]

Doctor, Mobic is a non-steroidal anti-inflammatory drug – an NSAID – that inhibits both COX-1 and COX-2 at its therapeutic doses. It does not selectively inhibit COX-2.

If the doctor continues and asks how Mobic differs from VIOXX, respond:

> Doctor, VIOXX is indicated for the signs and symptoms of OA, acute pain in adults, and primary dysmenorrhea. Mobic is indicated for OA. VIOXX is available in three tablet strengths, 12.5 mg, 25 mg, and 50 mg, which allows you to prescribe VIOXX one tablet, once daily for all indications. Mobic is available in a 7.5 mg tablet; to increase the dose requires two 7.5 mg tablets. Finally, the two OA doses of VIOXX – 12.5 mg and 25 mg – are priced the same. The highest dose of Mobic is twice as expensive as the lowest dose because patients must take two tablets.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Alternatively, if the doctor continues and asks how Mobic's mechanism of action that you just explained differs from that of VIOXX, respond:

> Doctor, VIOXX is an NSAID that inhibits COX-2 without inhibiting COX-1 at therapeutic doses. Of course, Doctor, we would not recommend that you base your prescribing decision on the mechanism of action of the drug. Can I take a minute and share with you the clinical data on the Strength, Safety, and QD Simplicity of VIOXX?

~~Transition back to the HI COXIB or HI NSAID messages for VIOXX.~~

[redacted]

Doctor, if cost is your reason for considering Mobic, let me point out that Mobic is available only in a 7.5mg tablet. That means that if you need to increase your patients dose to 15mg, the maximum recommended dose for OA, your patients cost will double. In contrast, VIOXX 12.5 and 25 mg tablets are flat priced so you can select the appropriate dose for your OA patients without regard to cost.

Let me share with you the benefits that VIOXX can provide for you and your patients.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Remember to provide appropriate balancing information as part of all product discussions.

Be impressed with MOBIC's tremendous amount of worldwide experience

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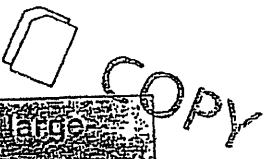
Doctor, I can understand that experience with a medication is very important to you. The most valuable experience is not just what has happened abroad, but the clinical experience that you and your colleagues have developed on your own. What has been your experience with VIOXX over the last year? Have you been satisfied with your clinical experience using VIOXX over the last year?

In the last year, VIOXX has achieved a vast amount of clinical experience among many specialties-Rheumatologists, Orthopedic Surgeons, Gastroenterologists, Internists, and Primary Care Physicians. VIOXX has become second most prescribed branded NSAID in the U.S. in less than one year. Is this the kind of experience that is important to you?

Not only has VIOXX developed a tremendous amount of clinical experience within the U.S., but VIOXX has been extensively studied in clinical trials. Let me share some data with you demonstrating the safety and efficacy of VIOXX.

Transition back to the HI COXIB or HI NSAID messages for VIOXX. Be sure to emphasize the data within your Core Visual Aid as you deliver these messages. Focus on the number of patients within each study and the benefit which the results present for the doctor's patient.

Remember to provide appropriate balancing information as part of all product discussions.



[redacted]

Doctor, I can understand that when choosing a medication to treat your OA patients, you would want to choose a medication with a well documented GI safety and tolerability profile.

Doctor, the studies which you're referring to are not reflected in the prescribing information for MOBIC. I believe that those studies only lasted 28 days, did not include endoscopic data, and only included the 7.5mg dose of MOBIC.

Let me remind you of the extensive GI data available for VIOXX. In two studies involving over 1500 patients, VIOXX demonstrated significantly fewer endoscopic ulcers than ibuprofen and was consistent across all studies. These studies lasted 6 months, and the incidence rate of ulcers in groups receiving VIOXX did not increase over time. These studies were done with the 25mg and 50mg dose of VIOXX, although I want to remind you that the 25mg dose is the maximum recommended dose for chronic OA.

Does the duration and inclusion of endoscopy data in the VIOXX studies cause you to be more impressed with the data for VIOXX than that of MOBIC?

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Remember to provide appropriate balancing information as part of all product discussions.

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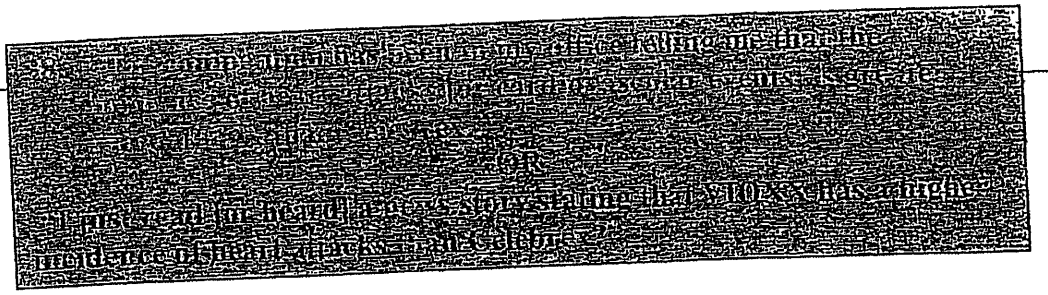

Doctor, there are no head-to-head studies comparing the cardiovascular profile of the two drugs. As a result, you cannot compare the drugs and conclude that one drug had fewer events than the other. What you may be referring to is press reports of the incidence rates in two separate studies. In the VIOXX GI Outcomes Trial (VIGOR), the incidence of MI was 0.4% with VIOXX and 0.1% with naproxen. Upon further analysis, four percent of patients in the VIOXX GI Outcomes Study had experienced a cardiac event such as a heart attack or stroke before entering the study and thus met the established criteria for the use of aspirin for secondary CV prophylaxis. In the remaining 96% of patients for whom aspirin was not indicated for secondary CV prophylaxis, the incidence of MI was lower—0.2% for VIOXX and 0.1% for naproxen. This difference was not statistically significant.

In a separate GI outcomes trial of Celebrex, the CLASS study, Searle has reported that the incidence of MI was 0.5% with Celebrex, 0.3% with diclofenac, and 0.5% with ibuprofen. They also presented data for patients who were not prescribed aspirin. In this group, the incidence of MI was 0.2% for Celebrex and 0.1% for the comparator NSAIDs Again, doctor, I want to emphasize that the results of two different studies can't be compared, and that's particularly true here when you have studies of differing duration and in different patient populations.

If needed, continue to address the physicians concerns with the cardiovascular effects of VIOXX by guiding them through the Cardiovascular Card as outlined in Roadmap for the CV Card.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

NOTE: There will be an additional PIR to address these issues available shortly.

If the doctor asks you further for the incidence of MI from the OA studies presented in the package insert for VIOXX tell them,

In the clinical OA trials for VIOXX reported in our package insert, the incidence of MI was less than 0.1% with VIOXX.

If needed, continue to address the physicians concerns with the cardiovascular effects of VIOXX by guiding them through the Cardiovascular Card as outlined in Roadmap for the CV Card.

Transition back to the HI COXIB or HI NSAID messages for VIOXX.

Remember to provide appropriate balancing information as part of all product discussions.